Original Article

Statin use and all-cause and cancer mortality: BioBank Japan cohort

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Hiroshi Yokomichi [a, *], Akiko Nagai [b], Makoto Hirata [c], Akiko Tamakoshi [d], Yutaka Kiyohara [e], Yoichiro Kamatani [f], Kaori Muto [b], Toshiharu Ninomiya [g], Koichi Matsuda [h], Michiaki Kubo [i], Yusuke Nakamura [h], BioBank Japan Cooperative Hospital Group[j], Zentaro Yamagata [a]

[a] Department of Health Sciences, University of Yamanashi, Yamanashi, Japan
[b] Department of Public Policy, Institute of Medical Science, The University of Tokyo, Tokyo, Japan
[c] Laboratory of Genome Technology, Institute of Medical Science, The University of Tokyo, Tokyo, Japan
[d] Department of Public Health, Hokkaido University Graduate School of Medicine, Sapporo, Japan
[e] Hisayama Research Institute for Lifestyle Diseases, Fukuoka, Japan
[f] Laboratory for Statistical Analysis, RIKEN Center for Integrative Medical Sciences, Yokohama, Japan
[g] Department of Epidemiology and Public Health, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan
[h] Laboratory of Molecular Medicine, Institute of Medical Science, The University of Tokyo, Tokyo, Japan
[i] RIKEN Center for Integrative Medical Sciences, Yokohama, Japan

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ABSTRACT

Background: Statins are the first-line agents used to treat patients with high serum low-density lipoprotein cholesterol levels, thus reducing the risk of death from arterial sclerotic cardiovascular disease; however, little is known about the effects of non-statin pharmacological interventions on mortality as well as about the potential protective effects of statin use against cancer death. This work aimed to compare all-cause and cancer mortality among patients with hyperlipidaemia who did and did not receive statin treatment.
Methods: Between 2003 and 2007 fiscal years, we recruited Japanese patients diagnosed with hyperlipidaemia from 66 hospitals. Patients in our cohort were followed up for a maximum of 12 years to observe the causes of death. Kaplan–Meier estimates from the baseline were used to compare the mortality of patients based on the administered medicine. All-cause mortality were compared among patients with/without administration of statins and other agents; any-organ and colorectal cancer mortality were compared between patients with/without administration of statins.
Results: Our cohort included 41,930 patients with mean ages of 64–66 years and mean body mass indices of 24–25 kg/m^2. Patients who received statin monotherapy and were treated with lifestyle modification exhibited nearly identical survival curves, whereas statin use represented a non-significant but potentially protective effect against colorectal cancer-related mortality. The lowest mortality in this cohort was associated with resin monotherapy.
Conclusions: Mortality rate has been similar for patients treated with statin monotherapy and lifestyle modification. Statin monotherapy could potentially reduce any-organ- and colorectal cancer-related mortality.

Introduction

Arterial sclerotic cardiovascular disease (ASCVD) is a leading cause of death worldwide. Among the available pharmacological interventions, evidence has established the ability of hydroxymethyl glutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) in reducing the risk of ASCVD by lowering serum levels of

* Corresponding author. Department of Health Sciences, University of Yamanashi, 1110 Shimokato, Chuo City, Yamanashi, 4093898, Japan.
E-mail address: hyokomichi@yamanashi.ac.jp (H. Yokomichi).
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[j] BioBank Japan Cooperative Hospital Group are listed in Appendix.

low-density lipoprotein cholesterol (LDL-C).[1] For instance, a recent meta-analysis of statin use reports associated odds ratios of 0.70 for major coronary events, 0.81 for major cerebrovascular events and 0.88 for all-cause mortality.[2] Consequently, statins have achieved the status of first-line agents for the treatment of patients with high serum levels of LDL-C.[3–5]

Over the past few decades, researchers have sought candidate second-line agents, leading to the clinical introduction of several pharmacological agents. Among these, ezetimibe,[6] resin (bile acid sequestrants, i.e. cholestyramine, colestipol and colesevelam),[7] fibrate,[8,9] nicotinic acid,[10] probucol[11,12] and polyunsaturated fatty acids[13,14] (e.g. eicosapentaenoic acid [EPA][15] and docosahexaenoic acid [DHA]) have been investigated; however, little is known about the mortality rate in patients with the use of these agents.

Additional reports have described anti-cancer properties of statins with respect to the HMG-CoA reductase pathway[16] as well as cellular proliferation and migration[17]; however, the existing epidemiologic data regarding the protective effects of statin against cancer incidence and mortality are inconclusive.[18–23] Accordingly, the present study aimed to compare mortality in a multi-regional hospital-based cohort of patients who did and did not use statins and determine the all-organ- and colorectal cancer-associated mortality within our cohort.

Methods

Hyperlipidaemic patient cohort

We initially established the baseline time point using data from the BioBank Japan Project, which had registered 200,000 patients with 47 diseases between 2003 and 2007 fiscal years.[24] Details of this cohort have been published elsewhere.[25–27] We collected annual information on survival, mortality and causes of death from patients' medical records, the residence registry and data from the Vital Statistics Act.[28]

For this study, we registered more than 40,000 Japanese patients who had received a physician's diagnosis of dyslipidaemia at one of the 66 participating hospitals. To research the cumulative mortality associated with pharmacological interventions, we limited the patient age to ≥40 years. Moreover, to determine the overall mortality risk, we analysed patients with both primary and secondary dyslipidaemia (e.g. dyslipidaemia due to lifestyle factors, hypothyroidism, nephrosis syndrome, diabetes, primary biliary cirrhosis, obstructive jaundice, Cushing syndrome, drug-induced hyperlipidaemia, uraemia, systemic lupus erythematosus, alcohol consumption and obesity).

Measurements

Serum samples and information from medical records were collected for each patient upon enrolment. Serum LDL-C levels were indirectly estimated using the Friedewald equation,[29] which is considered more precise than direct measurement[30] in accordance with the Japanese guideline.[5] We estimated the non-HDL-C level as the serum total cholesterol level minus the high-density lipoprotein (HDL-C) level. Body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in metres. Coronary artery disease (CAD) included myocardial infarction and stable or unstable angina pectoris. Chronic kidney disease was defined as an estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 m^2 at registration, although the guideline for clinical practice requires maintenance of this low level for ≥3 months.[31] Chronic respiratory disease included asthma, chronic obstructive pulmonary disease, interstitial pneumonia, pulmonary fibrosis and pneumoconiosis. Cancer included that of all

organs. Causes of death were identified according to the International Statistical Classification of Diseases and Related Health Problems (ICD-10).[27,32]

Statistical analysis

We report herein the mean values [standard deviations (SDs)] for age, BMI, serum LDL-C, HDL-C, triglycerides (TG), non-HDL-C, glycaemic control and blood pressure in dyslipidaemic patients according to the status of statin-based pharmacological intervention. Moreover, we also present the distributions of sex, smoking, alcohol consumption and various comorbidities. To examine the mortality risks of patients who did and did not receive medication therapy, we depicted Kaplan–Meier estimates (i.e., estimated survival curves),[33] which were subjected to a statistical comparison using the log-rank test.[34] We compared the estimated survival curves of the patients who received statin, polyunsaturated fatty acid or resin monotherapy and those who did not receive any medication.

To address the secondary interest of this work, we explored the cancer mortality-related survival curves of patients treated with and without statin monotherapy among patients with no previous or current history of cancer at the baseline. We performed a cancer-related mortality analysis after stratifying patient deaths according to cancer in any organ and colorectum. Hence, patients in the former analysis who were lost to follow-up or died from any non-cancer diseases and those in the latter analysis who were lost to follow-up or died of non-colorectal cancer diseases were censored. Because we explored the natural histories of the patients with various profiles for which physicians and patients selected pharmacological interventions, we performed these crude survival analyses.

To confirm the above-mentioned crude survival analyses, we calculated the hazard ratios of each pharmaceutical intervention using crude and multivariable Cox proportional models.[35] The multivariable analyses adjusted for the following variables: sex; age; comorbidities of hypertension, coronary arterial disease, diabetes, chronic kidney disease, cerebrovascular disease, peripheral arterial disease, cancer and chronic respiratory disease; smoking and drinking statuses; daily walking habit and daily vegetable consumption. All statistical analyses were performed using the SAS statistical software (version 9.3; SAS Institute, Cary, NC, USA); the R statistical software (version 2.15.3; R Project for Statistical Computing, Vienna, Austria) was used to generate Kaplan–Meier estimates. All reported p values were two-sided; p values of <0.05 were considered to indicate statistical significance.

Ethical considerations

The ethics committees of the Institute of Medical Science, The University of Tokyo, RIKEN Center for Integrative Medical Sciences and 12 cooperating medical institutions approved the protocol of this study in accordance with the ethical guidelines and regulations of the Declaration of Helsinki. The Japanese guidelines permit the use of data from medical examinations and information without consent if data are anonymous. Hence, informed consent was not required for the present investigation.

Results

Patient characteristics

Table 1 shows the baseline characteristics of patients according to the use of statins and/or other medicines. Among patients in the statin monotherapy group (n = 18,904), the proportion of men was slightly smaller than that of the statin and other medicines

Table 1
Characteristics of patients with hyperlipidaemia according to the use of statins and other medications.

Baseline characteristics	Statin monotherapy (n = 18,904)	Statin and other medicines (n = 1495)	Other medicines (n = 2761)	No medication (n = 18,770)
Male, no. (%)	8974 (47.5)	774 (51.8*)	1640 (59.4*)	9647 (51.4*)
Age, years	65.8 (9.9)	65.9 (10.3)	64.3* (10.8)	64.6* (10.5)
Body mass index, kg/m^2	24.4 (3.5)	24.7* (3.6)	25.0* (3.8)	24.2* (3.6)
Low-density lipoprotein, mg/dL and mmol/L	117 (38) and 3.02 (0.97)	114* (36) and 2.95* (0.92)	123* (37) and 3.19* (0.96)	132* (39) and 3.41* (1.02)
High-density lipoprotein (HDL), mg/dL and mmol/L	57 (16) and 1.47 (0.42)	54* (18) and 1.40* (0.46)	52* (16) and 1.35* (0.42)	55* (17) and 1.43* (0.43)
Triglyceride, mg/dL and mmol/L	155 (109) and 1.75 (1.23)	186* (177) and 2.10* (1.99)	200* (159) and 2.26* (1.80)	167* (124) and 1.88* (1.40)
Non-HDL, mg/dL and mmol/L	147 (40) and 3.80 (1.03)	149 (38) and 3.85 (0.98)	162* (37) and 4.18* (0.95)	164* (40) and 4.25* (1.04)
Glycated haemoglobin A1c, % and mmol/mol	6.4 (1.3) and 47 (15)	6.5 (1.3) and 47 (14)	6.4 (1.2) and 46 (13)	6.4 (1.3) and 47 (14)
Systolic blood pressure, mm Hg	132 (16)	132 (16)	134* (16)	133* (17)
Diastolic blood pressure, mm Hg	76 (10)	77 (11)	78* (11)	78* (11)
Smoking, never/ex-/current, no.	10,459/5378/3067	780/433/282	1367/771/623	11,116/4408/3246
Current drinker, no. (%)	5990 (31.7)	508 (34.0)	1107 (40.1*)	5989 (31.9)
Comorbidity and past history, no. (%)				
Coronary arterial disease	5866 (31.0)	490 (32.8)	508 (18.4*)	4230 (22.5*)
Diabetes mellitus	5669 (30.0)	479 (32.0)	944 (34.2*)	5415 (28.9*)
Chronic kidney disease	6028 (31.9)	487 (32.6)	957 (34.7*)	7032 (37.5*)
Cerebrovascular disease	2498 (13.2)	247 (16.5*)	383 (13.9)	2148 (11.4*)
Peripheral arterial disease	425 (2.3)	71 (4.8*)	73 (2.6)	369 (2.0)
Cancer	1280 (6.8)	92 (6.2)	164 (5.9)	1609 (8.6*)
Chronic respiratory disease	951 (5.0)	72 (4.8)	159 (5.8)	1004 (5.4)

Asterisks denote statistical significance at a p level <0.05 vs. statin monotherapy.

Survival curves of hyperlipidaemic patients according to statin use
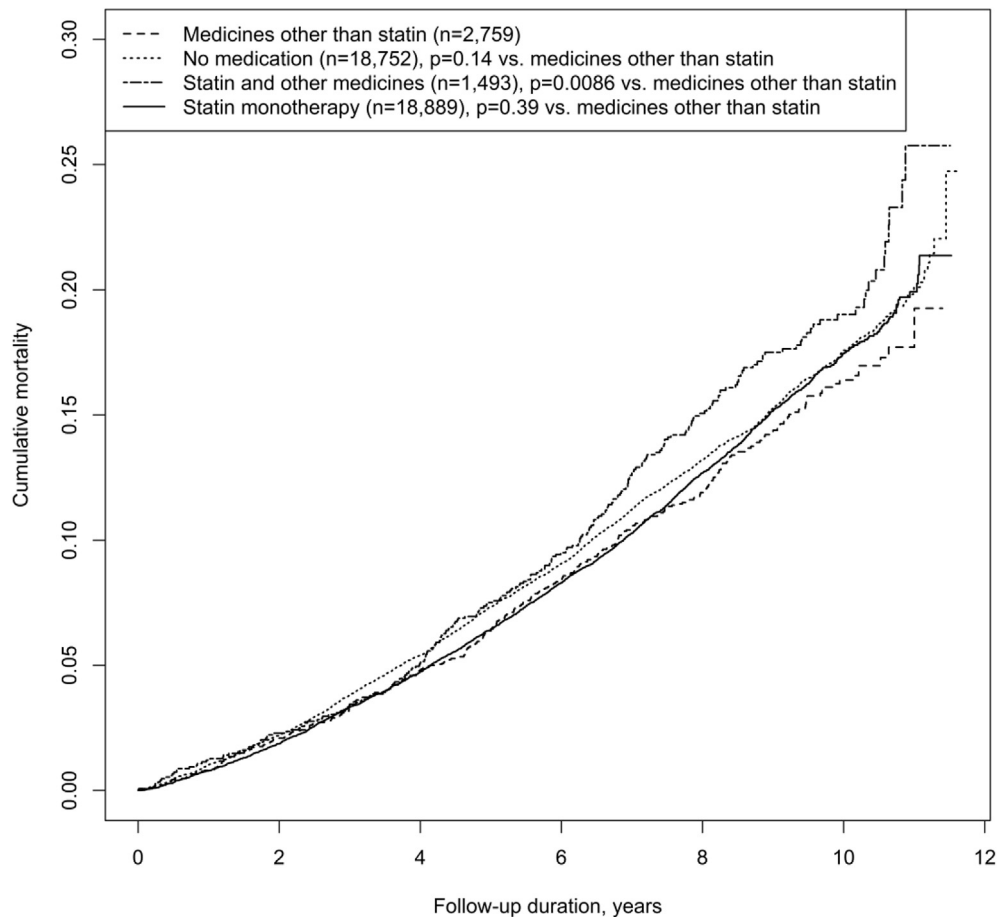
Fig. 1. Survival curves of patients with hyperlipidaemia with/without statin use.

(n = 1495), other medicines (n = 2761) and no medication (n = 18,770) groups. The mean ages and BMI values of the four groups ranged from 64 to 66 years and from 24 to 25 kg/m², respectively. The serum cholesterol levels in the statin monotherapy group were as follows: LDL-C, 117 (SD: 38) mg/dL; HDL-C, 57 (SD: 16) mg/dL; TG, 155 (SD: 109) mg/dL and non-HDL-C, 147 (SD: 40) mg/dL. The corresponding values were 114 (SD: 36), 54 (SD: 18), 186 (SD: 177) and 149 (SD: 38) mg/dL, respectively, in the statin and other medicines group; 123 (SD: 37), 52 (SD: 16), 200 (SD: 159) and 162 (SD: 37) mg/dL, respectively, in the other medicines group; and 132 (SD: 39), 55 (SD: 17), 167 (SD: 124) and 164 (SD: 40) mg/dL, respectively, in the no medication group. Chronic kidney disease was the most frequent comorbidity in the four medication groups.

Survival analyses

Fig. 1 presents observed survival curves of the four medication groups, beginning at the baseline. The following total numbers of deaths were recorded: 2619 in the statin monotherapy group (p for log-rank test = 0.39 vs. other medicines group), 249 in the statin and other medicines group (p for log-rank test = 0.0086 vs. other medicines group), 363 in the other medicines group and 2651 in the no medication group (p for log-rank test = 0.14 vs. other medicines group). Overall, the statin and other medicines group

and other medicines group were observed to have the shortest and longest survival durations, respectively.

Fig. 2 presents the observations of a survival analysis according to single-agent administration, with the following numbers of deaths: 64 in the polyunsaturated fatty acid monotherapy group (for log-rank test = 0.72 vs. statin monotherapy group), 13 in the resin monotherapy group (p for log-rank test = 0.0078 vs. statin monotherapy group) and 2651 in the no medication group (p for log-rank test = 0.22 vs. statin monotherapy group). Among patients followed for 3−8 years, the resin monotherapy group was observed to have the longest survival time, followed by the statin monotherapy, no medication and polyunsaturated fatty acid monotherapy groups. Among those followed for ≥9 years, no difference was observed in the survival curves of the statin monotherapy, polyunsaturated fatty acid monotherapy and no medication groups.

Figs. 3 and 4 present observed survival curves for cancer and colorectal cancer mortality, respectively, among statin and non-statin users. Data reported 498 and 560 deaths from cancer in any organ in the statin monotherapy and no statin use groups, respectively (p for log-rank test = 0.66). Furthermore, 41 and 53 deaths from colorectal cancer were reported in the statin monotherapy and no statin use groups, respectively (p for log-rank test = 0.43). Although patients treated with and without statins did not differ significantly with respect to survival in either analysis, the patients with hyperlipidaemia in the statin monotherapy

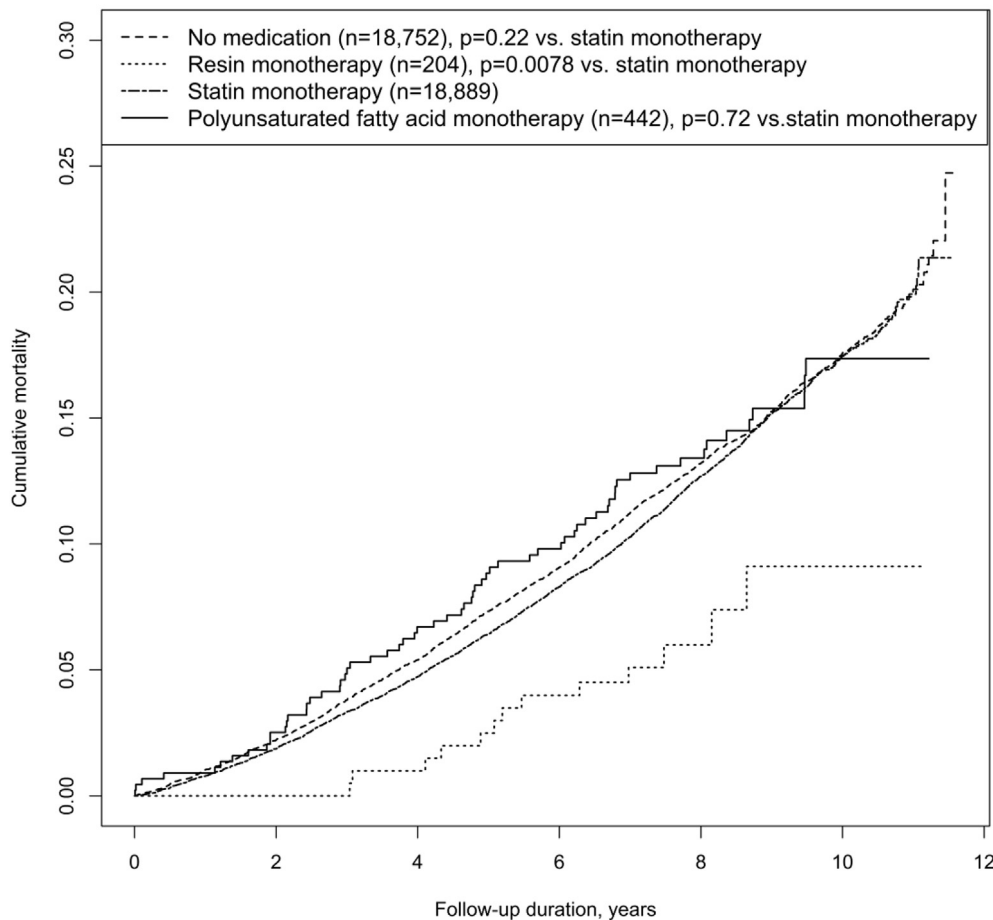Survival curves of hyperlipidaemic patients treated with single agents

Fig. 2. Survival curves of patients with hyperlipidaemia treated with single agents.

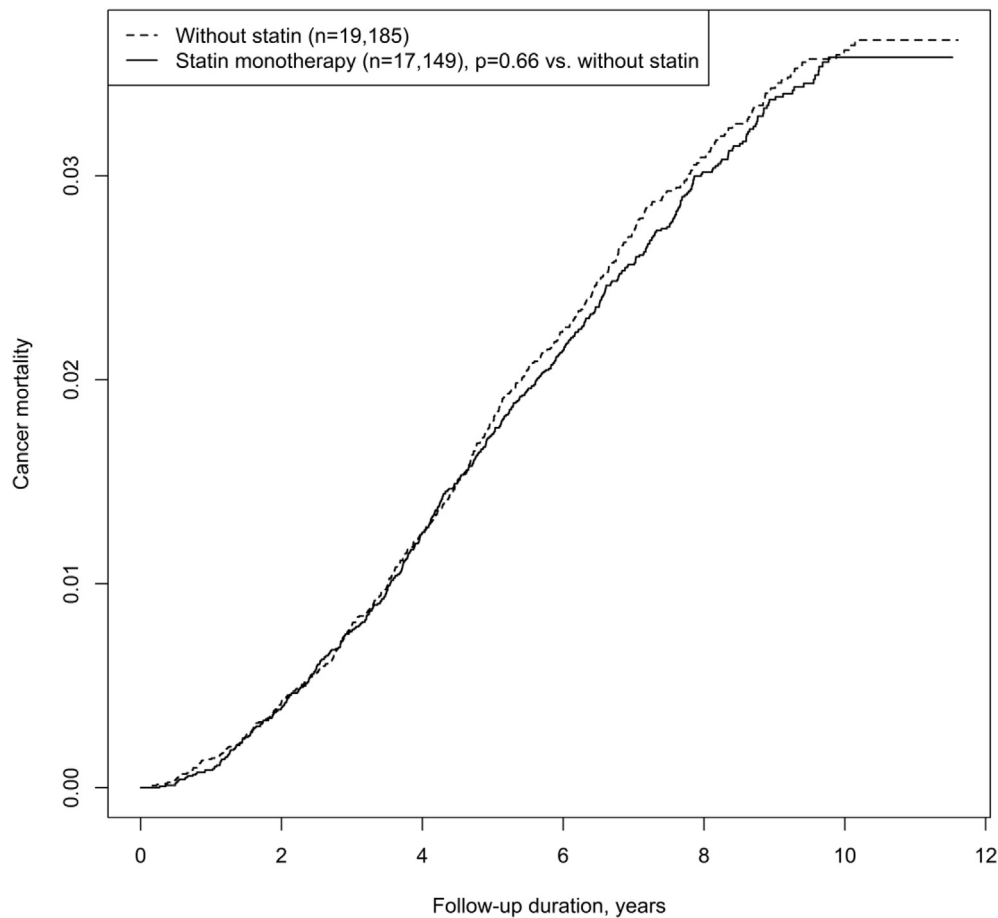Survival curves of hyperlipidaemic patients according to statin use

Fig. 3. Any-organ cancer mortality in patients with hyperlipidaemia with/without statin use.

group appeared to have lower mortality than those in the no statin use group.

Table 2 shows the estimated hazard ratios from the crude and multivariable Cox proportional hazard models; these correspond to the crude analyses of survival curve (Figs. 1–4). Statin monotherapy barely increased the cumulative mortality (i.e., no statistical significance) compared with the use of other medicines. Among the compared monotherapies, resin use was potentially the most protective with respect to cumulative mortality, although this difference was not statistically significant. Compared with non-statin treatment, statin monotherapy exhibited potentially protective effects on any-organ and colorectal cancer mortality, although these differences were not statistically significant.

Discussion

Summary

Our data suggest that, when measured from the baseline, patients treated with statin and other medicines had a higher rate of mortality at ≥5 years compared with those treated with either statin monotherapy, other medicines or no medication. Additionally, the patients treated with resin had the lowest rate of mortality among those treated with monotherapies or no medication. Interestingly, patients treated with statins had a lower rate of any-organ and colorectal cancer-related mortality compared with those not treated with statins, although these differences were not statistically significant.

Interpretation in the context of previous studies

Despite the lack of statistical significance, the observation that patients in the other medicines group had the lowest rate of mortality (Fig. 1 and Table 2) may be attributed to a likely state of mild hyperlipidaemia during the period of 2003–2007, when administering statins were not yet considered as the first-line treatment. The propensity to select medicines other than statins for patients with mild hyperlipidaemia may have led to this outcome. In contrast, the patients in the statin and other medicines group might have been suffering from severe hyperlipidaemia and may have failed to achieve the desired goal with monotherapy.[7] Furthermore, it is interesting that the resin monotherapy group exhibited a lower rate of mortality than the statin monotherapy group and the lowest rate among the four single-agent administration groups (Fig. 2 and Table 2). As mentioned previously, physicians should likely have administered resin, which was known to have more moderate effects relative to statins, to patients with very low-grade hyperlipidaemia.[7]

In the cancer mortality analysis, we observed no apparently protective or harmful effect of statin therapy (Figs. 3 and 4 and Table 2). Two meta-analyses issued in 2006–2007 found no relationship between statin use and cancer incidence[21,23]; however, the

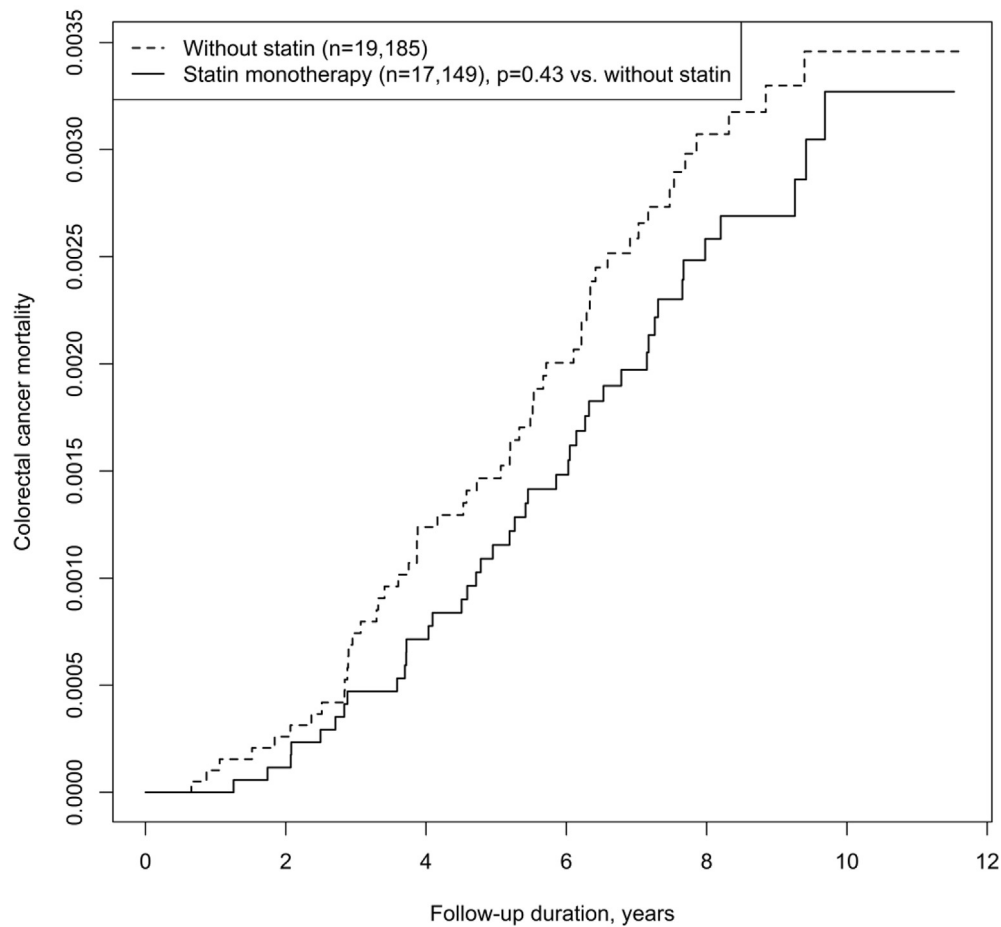## Survival curves of hyperlipidaemic patients according to statin use

Fig. 4. Colorectal cancer mortality in patients with hyperlipidaemia with/without statin use.

Table 2
Crude and adjusted hazard ratios (HRs) for mortality of all-cause, cancer and colorectal cancer in patients with hyperlipidaemia with/without statin use.

Medication	Crude HR (95% CI)	p value	Adjusted HR[a] (95% CI)	p value
Cumulative mortality				
Statin monotherapy (n = 18,889)	1.05 (0.94—1.18)	p = 0.39	1.05 (0.93—1.17)	p = 0.45
Statin and other medicines (n = 1493)	1.19 (1.01—1.41)	p = 0.044	1.10 (0.93—1.30)	p = 0.28
No medication (n = 18,752)	1.08 (0.96—1.21)	p = 0.18	1.15 (1.03—1.29)	p = 0.016
Medicines other than statin (n = 2759)	Ref		Ref	
Cumulative mortality for treatment with a single agent				
Statin monotherapy (n = 18,889)	Ref		Ref	
Polyunsaturated fatty acid monotherapy (n = 442)	1.07 (0.83—1.38)	p = 0.60	0.99 (0.77—1.29)	p = 0.97
Resin monotherapy (n = 204)	0.43 (0.23—0.80)	p = 0.0080	0.60 (0.32—1.11)	p = 0.10
No medication (n = 18,752)	1.03 (0.97—1.09)	p = 0.33	1.10 (1.04—1.17)	p = 0.0009
Cancer mortality				
Statin monotherapy (n = 17,149)	0.93 (0.82—1.05)	p = 0.24	0.89 (0.78—1.01)	p = 0.076
Without statin (n = 19,185)	Ref		Ref	
Colorectal cancer mortality				
Statin monotherapy (n = 17,149)	0.75 (0.49—1.14)	p = 0.18	0.71 (0.46—1.08)	p = 0.11
Without statin (n = 19,185)	Ref		Ref	

[a] Hazard ratios were adjusted for the following variables: sex; age; comorbidities of hypertension, coronary arterial disease, diabetes, chronic kidney disease, cerebro-vascular disease, peripheral arterial disease, cancer and chronic respiratory disease; smoking and drinking statuses; daily walking habit and daily vegetable consumption.

results of our survival analysis appear to agree with a study from Danish national data that reported the effects of statin use against cancer mortality in 2012.[18] For colorectal cancer mortality, a 2010 meta-analysis of randomised controlled trials concluded a non-significant but modestly protective effect of statins.[20] A 2015 pharmacological intervention study, sourced from Japanese health insurance claims and spontaneous reports, found that statin use increased the risk of colorectal cancer.[19] Our Japanese hospital-based data suggest the safety of statin use in terms of colorectal cancer mortality, although our study is not experimental but observational, and the rarity of death events may have led to insufficient statistical power.

Implications for clinical practice

Little difference in survival was observed between the statin monotherapy and no medication groups; however, the patients who were not treated with medication were thought to have low-grade hyperlipidaemia, and were therefore, recommended to make lifestyle modifications. This inference leads to the thought that statin monotherapy for targeted patients and lifestyle modification without medication for patients with low-grade hyperlipidaemia may yield similar efficacies as observed by this study. In addition, statin monotherapy has shown similar or lower cancer mortality risk than non-statin therapy. These results are reassuring and support the continued use of statins as a first-line agent for the treatment of hyperlipidaemia.

Limitations and strengths

We should consider several limitations when interpreting this work. First, the patients were already receiving individualised treatments at the baseline; accordingly, the baseline lipid profiles were recorded after receiving the treatment. Ideally, the analysis would have been initiated at the time of treatment onset or the patient's first visit. This limitation might have attenuated the impact of our analysis of survival time from the baseline; however, we consider that this work is a worthy example of a natural observation of dyslipidaemic patients treated with various medications. Second, we did not include ezetimibe, fibrate, nicotinic acid and probucol in our analysis for the effects of single-agent administration on mortality due to insufficient sample sizes. Third, in the survival analyses, we did not consider the competing risk of morality. Losses to follow-up were censored in a non-informative manner, whereas competing risk events were censored in an informative manner.[36,37] This practice would bias the observed differences in mortality among medication groups towards unknown directions. Last, the physicians might have changed the treatments in the follow-up period. These changes in treatments may have attenuated the observed differences in mortality between medication groups.

In contrast, we would like to highlight several strengths of this work. First, because the Japanese guidelines available from 2003 to 2007 did not recommend statins as a first-line agent for lowering serum LDL-C levels, we were able to analyse mortality among patients treated with medicines other than statin. This situation allowed us to compare the survival of patients treated with and without statins, although the lack of random allocation could not allow us to estimate the effect of medications; in other words, the absence of a first-line agent in the 2000s enabled us to observe the natural survival histories of patients treated with each available medication. Second, the sample size of this study was extremely large, and we could accordingly analyse mortality among the relatively rare patients treated with resin or polyunsaturated fatty acid monotherapy. Third, this work is the first to explore the cancer mortality risk in the presence or absence of statin therapy among Japanese patients diagnosed with hyperlipidaemia in a hospital setting, although the small number of fatal events led to non-statistically significant results. We believe that the data presented in Fig. 4 provide an epidemiologic answer to the question regarding the potential preventive effects of statin on colorectal mortality.

Conclusions

Our multi-regional observational study has suggested that statin monotherapy would be effective with regard to all-cause and cancer mortality. In particular, when colorectal cancer mortality was considered, statin use has exhibited a non-significant but potentially protective effect. Finally, resin use has been associated with the lowest mortality, although we need to carefully interpret this result as the patients treated with resin monotherapy might have been biased towards a low-grade hyperlipidaemic state.

Author contributions

MK and ZY conceived the study, whereas HY and ZY designed the study. HY performed the statistical analysis and wrote the manuscript. AN, TN, YK and MH researched the data. All authors contributed to the discussion and reviewed and edited the manuscript. MK and ZY are the guarantors of this work, had full access to all data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

Conflicts of interest

None declared.

Appendix. Author list for BioBank Japan Cooperative Hospital Group

Members of medical institutions cooperating on the BioBank Japan Project who co-authored this paper include Kazuo Misumi, Nobuyoshi Higa, Sunao Matsubayashi and Kei Matsuura (Tokushukai Hospitals); Shiro Minami, Hitoshi Sugihara and Naoya Emoto (Nippon Medical School); Hirotoshi Ohmura, Akihiro Inui and Michihiro Ogasawara (Juntendo University); Satoshi Asai, Mitsuhiko Moriyama and Yasuo Takahashi (Nihon University); Tomoaki Fujioka and Wataru Obara (Iwate Medical University); Seijiro Mori and Hideki Ito (Tokyo Metropolitan Institute of Gerontology); Satoshi Nagayama and Yoshio Miki (The Cancer Institute Hospital of JFCR); Akihide Masumoto and Akira Yamada (Aso Iizuka Hospital); Yasuko Nishizawa and Ken Kodama (Osaka Medical Center for Cancer and Cardiovascular Diseases); Satoshi Ugi and Hiroshi Maegawa (Shiga University of Medical Science); Yukihiro Koretsune and Hideo Kusuoka (National Hospital Organization, Osaka National Hospital) and Masako Ueyama (Fukujuji Hospital).

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