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CLINICAL RESEARCH
Diabetes and metabolic disorders

Acromegaly and cardiovascular outcomes: a cohort study

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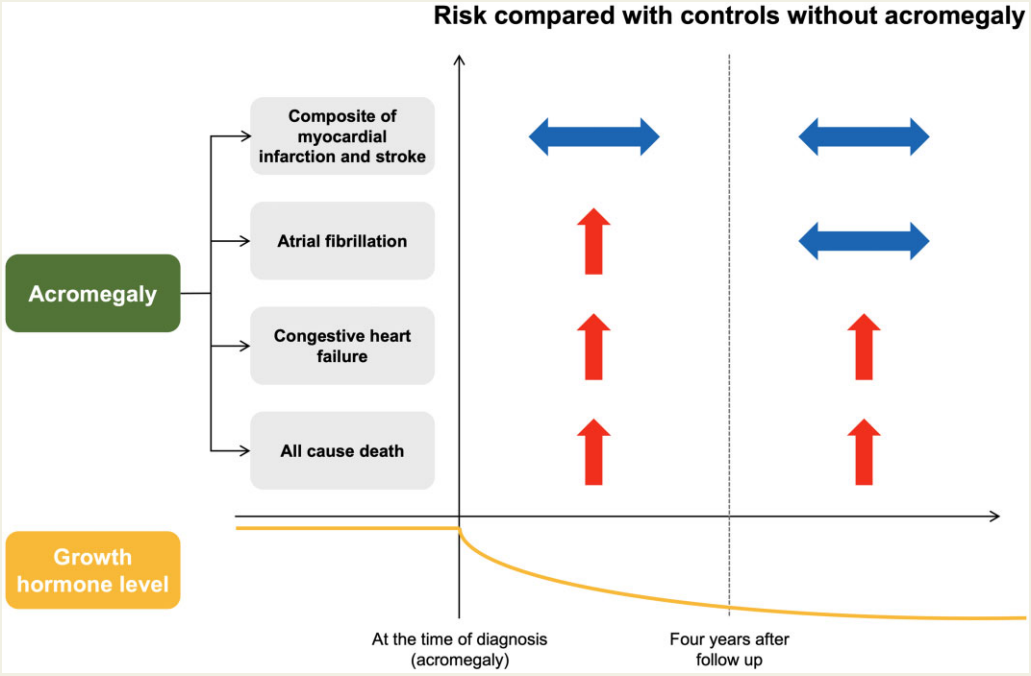
Graphical Abstract



Time-dependent changes in the association between acromegaly and cardiovascular disease after treatment.

Aims Cardiovascular disease is a common complication in acromegaly. We investigated the risk of cardiovascular disease and mortality in patients with acromegaly in a large-scale population using nationwide data in Korea.

Methods and results We performed a nationwide, retrospective, observational, cohort study of patients with acromegaly ($n = 1874$) and age- and sex-matched subjects without acromegaly ($n = 9370$) for a mean follow-up of 7.5 ± 3.2 years. The study outcomes were myocardial infarction, stroke, atrial fibrillation, congestive heart failure, and all-cause death. All outcomes were analysed by Cox proportional hazards regression analysis while controlling for age, sex, household income, place, Type 2 diabetes, hypertension, and dyslipidaemia. The incidence (per 1000 person-years) of atrial

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fibrillation (3.06 vs. 1.70; $P = 0.001$), congestive heart failure (3.11 vs. 1.63; $P < 0.001$), and all-cause mortality (6.31 vs. 4.03; $P < 0.001$) in patients with acromegaly was higher than in controls. However, the incidence of myocardial infarction and stroke did not differ between groups. After adjustment for covariates, the risk for atrial fibrillation [hazard ratio (HR): 1.59; 95% confidence interval (CI): 1.09–2.31], congestive heart failure (HR: 1.54; 95% CI: 1.06–2.25), and all-cause mortality (HR: 1.31; 95% CI: 1.01–1.69) was significantly higher in patients with acromegaly. In time lag sensitivity analysis, a higher risk for atrial fibrillation was observed only in the first 4 years after diagnosis in acromegaly patients compared with controls (HR: 3.05; 95% CI: 1.94–4.79).

Conclusion Patients with acromegaly were at higher risk for atrial fibrillation, congestive heart failure, and all-cause death. The risk of atrial fibrillation had a time-dependent association with acromegaly.

Keywords Acromegaly • Atrial fibrillation • Congestive heart failure • Mortality • Myocardial infarction • Stroke

Introduction

Acromegaly is characterized by chronic elevation of growth hormone (GH) and insulin-like growth factor-1 (IGF-1) as well as enlargement of organs and soft tissues.[1,2] A meta-analysis of 16 studies in 2008 showed that acromegaly is associated with an overall 72% increase in mortality compared with the general population.[3] Acromegaly is also associated with established risk factors for cardiovascular disease, such as hypertension, diabetes, and dyslipidaemia.[4] Moreover, excess GH may directly trigger cardiac abnormalities.[5] Cardiovascular disease is not only the most frequent comorbidity in patients with acromegaly (80% of cases) but also the most common cause of death (~50% of cases).[6] Some clinical studies that included echocardiography reported increased frequencies of left ventricular hypertrophy, diastolic dysfunction, and coronary heart disease[7,8] and others reported increased frequencies of valvular disease, arrhythmias, and cerebrovascular disease.[9,10]

Over the last two decades, use of radiotherapy in acromegaly has decreased and the implementation of surgery and medical therapy has increased in many centres.[11,12] This strategy has resulted in decreased mortality rate and a change in the prognosis of different acromegaly complications with better disease control.[11,12] However, there are few recent data for cardiovascular disease complications in patients with acromegaly.

In this observational, analytical, retrospective, and controlled study, we investigated the risk of myocardial infarction, stroke, atrial fibrillation, congestive heart failure, and all-cause death in patients with acromegaly in a large-scale population dataset from the National Health Information Database (NHID).

Methods

Study database

The data for our analysis were from the NHID, a public database on health care utilization and health screening that contains longitudinal data for 97% of the Korean population with linkage to the National Death Registry, the national health screening programme, and the rare incurable disease registry.[13,14] In South Korea, the term 'rare incurable disease' applies to diseases affecting fewer than 20 000 patients, or for which the affected number is unknown because diagnosis of the disease is difficult, which is determined according to the procedures and standards prescribed by Ordinance of the Ministry of Health and Welfare based on the 'Rare Disease Management Act' (see Supplementary material online, *Table S1*).[15,16] The targeted rare diseases (see Supplementary material online, Additional file 1) covered by the policy are determined via expert consultation based on their rarity and severity. Since 2009, the government has provided financial support by reducing the medical expenses of rare incurable patients through the National Health Insurance Service (NHIS).[16] Only patients who meet the diagnostic criteria defined by Ordinance of the Ministry of Health and Welfare for each rare disease based on results of comprehensive medical tests, including imaging studies, biochemistry, immunology, smear, culture, histological examination, and clinical diagnosis by a physician, can be registered in the rare incurable disease registry. In the case of acromegaly, both acromegaly-compatible imaging (magnetic resonance imaging or computed tomography) and growth overproduction biochemistry results (proven by glucose tolerance test) are needed for registration in the rare incurable disease registry and obtaining the code (V112 for acromegaly) for financial support by reducing medical expenses. Approval for the study protocol was obtained from the Institutional Review Board of Kangbuk Samsung Hospital (KBSMC 2019-09-003), which waived the requirement for informed consent because personal identifying information was not accessed.

Study subjects

This was a national, observational, cohort study that included 11 244 subjects. We initially identified 2259 patients with acromegaly from NHID between 2006 and 2016. Of these, 14 patients were under 20 years of age, 84 patients had a history of myocardial infarction, 144 patients had previous stroke history, 50 patients showed atrial fibrillation, 87 showed congestive heart failure, and 6 patients lacked complete data; these patients were excluded from our study. Therefore, 1874 eligible subjects with acromegaly were included in the acromegaly group. Age- and sex-matched subjects without acromegaly ($n = 9370$) were randomly extracted and this group was five times the size of the acromegaly group.

Definitions of acromegaly and study outcomes (cardiovascular events and death)

Acromegaly was defined as a case in a patient who had a history of outpatient care or hospitalization based on both the International Classification of Diseases (ICD), the 10th Revision code (E22.0), and the code for financial support by reducing medical expenses (V112). The outcomes of the study were newly diagnosed myocardial infarction, stroke, atrial fibrillation, congestive heart failure, and all-cause death. Outcomes were defined based on a primary or a secondary diagnosis (ICD-10

Table 1 Baseline characteristics at time of diagnosis of patients with acromegaly and at the time of age and sex matching of controls without acromegaly

	Controls (n = 9370)	Patients with acromegaly (n = 1879)	P-Value
Age (years)	47.02 ± 12.46	47.02 ± 12.46	1
Men	4245 (45.3)	849 (45.3)	1
Urban	4447 (47.46)	888 (47.39)	0.9529
Household income			<0.0001
Basic livelihood security recipient	504 (5.38)	146 (7.79)	
Q1	1747 (18.64)	306 (16.33)	
Q2	1966 (20.98)	336 (17.93)	
Q3	2306 (24.61)	488 (26.04)	
Q4	2847 (30.38)	598 (31.91)	
Hypertension	1342 (14.32)	650 (34.69)	<0.0001
Type 2 diabetes	441 (4.71)	500 (26.68)	<0.0001
Dyslipidaemia	715 (7.63)	293 (15.64)	<0.0001

Values are given as mean ± standard deviation, or n (%).

codes): myocardial infarction (I21 or I22 in discharge diagnosis or these diagnostic codes documented at least twice in the outpatient records), stroke (I63 or I64 in discharge diagnosis and with claims for brain magnetic resonance imaging or brain computed tomography), congestive heart failure (I50 in discharge diagnosis), and atrial fibrillation (I48 in discharge diagnosis or more than twice in an outpatient clinic diagnosis). Death was defined using the National Death Registry. The study population was followed from baseline to the date of death, onset of cardiovascular event, or until 31 December 2018, whichever came first.

Comorbid metabolic diseases

Comorbid metabolic diseases in patients with acromegaly were analysed using the NHID. The presence of Type 2 diabetes mellitus was defined according to ICD-10 codes E11–14 and by a prescription for antidiabetic medication. The presence of hypertension was defined according to claims data for a prescription of antihypertensive medication under ICD-10 codes I10, I11, I12, I13, and I15. The presence of dyslipidaemia was defined according to the presence of claims data for a prescription of antihyperlipidaemic agents, under ICD-10 code E78.

Data analyses

Baseline characteristics were analysed using descriptive statistics. Categorical variables were described as frequency and percentage. Continuous variables were described as mean (± standard deviation) for normally distributed data. We compared baseline characteristics at time of diagnosis of patients with acromegaly and at time of 1:5 age matching and sex matching of controls without acromegaly. Continuous variables were compared using the independent samples t-test, while categorical variables were compared using the χ^2 test. The follow-up durations of the groups were obtained. The incidence rates of myocardial infarction, stroke, atrial fibrillation, congestive heart failure, and all-cause death were estimated for each group over the total follow-up period. Incidence curves were estimated by the Kaplan–Meier method, and the log-rank test was also conducted. All outcomes were analysed by Cox proportional hazards regression analysis while controlling for baseline covariates. We also conducted lag time sensitivity analysis by excluding the follow-up periods within the first 4 years. Levin's attributable risk, also referred to as the aetiological fraction, was calculated to estimate the proportion of deaths during follow-up that could be attributable to acromegaly.[17]

The null hypothesis was rejected for values of $P < 0.05$. Analyses were performed with SAS 9.4 (SAS Institute, Cary, NC, USA) and R program, version 3.4.1 (The R Foundation for Statistical Computing, Vienna, Austria, http://www.R-project.org).

Results

Baseline characteristics of subjects

Table 1 lists the baseline characteristics of the 1874 patients with acromegaly at the time of diagnosis and the 9370 age- and sex-matched controls at the time of matching. The mean age of the study subjects was 47.02 ± 12.46 years, and 45.3% of the study subjects were men. Compared with the control group, patients with acromegaly had a had a higher prevalence of hypertension (34.69% vs. 14.32%, P < 0.0001), Type 2 diabetes (26.68% vs. 4.71%, P < 0.0001), and dyslipidaemia (15.64% vs. 7.63%, P < 0.0001).

Acromegaly and cardiovascular events

Table 2 shows the cumulative prevalence, annual incidence, and hazard ratios (HRs) of outcomes in patients with acromegaly and controls. The composite outcome of myocardial infarction and stroke was identified in 45 (2.40%) patients with acromegaly and 185 (1.97%) controls during the mean follow-up period of 7.35 ± 3.27 years and 7.44 ± 3.22 years, respectively. *Figure 1A* presents the results of Kaplan–Meier survival analysis for the composite outcome of myocardial infarction and stroke. The incident rate of the composite outcome (myocardial infarction and stroke) was 3.27 per 1000 person-years in patients with acromegaly and 2.65 per 1000 person-years in controls; the rates were not different between the two groups (log-rank, $P = 0.207$). The risk for the composite outcome of myocardial infarction and stroke in patients with acromegaly was not higher than that of controls in multivariable Cox proportional hazards regression modelling after adjusting for age, sex, household income, place, Type 2 diabetes, hypertension, and

Table 2 Number, incidence rate, and hazard ratio of outcomes (myocardial infarction, stroke, atrial fibrillation, congestive heart failure, and all-cause death) in patients with acromegaly and controls

	No. patients	No. events	Duration (person-years)	Rate (events per 1000 person-years)	Hazard ratio (95% confidence interval)					
					Unadjusted	*P*-Value	Model 1	*P*-Value	Model 2	*P*-Value
Composite of myocardial infarction and stroke										
Controls	9370	185	69 757	2.65	1 (Ref.)	0.207	1 (Ref.)	0.196	1 (Ref.)	0.907
Acromegaly	1874	45	13 769	3.27	1.23 (0.89–1.71)		1.24 (0.90–1.72)		0.98 (0.69–1.39)	
Myocardial infarction										
Controls	9370	66	70 195	0.94	1 (Ref.)	0.813	1 (Ref.)	0.795	1 (Ref.)	0.361
Acromegaly	1874	14	13 895	1.01	1.07 (0.60–1.91)		1.08 (0.61–1.92)		0.75 (0.41–1.39)	
Stroke										
Controls	9370	126	69 955	1.80	1 (Ref.)	0.203	1 (Ref.)	0.188	1 (Ref.)	0.750
Acromegaly	1874	32	13 821	2.32	1.29 (0.87–1.90)		1.30 (0.88–1.91)		1.07 (0.71–1.62)	
Atrial fibrillation										
Controls	9370	119	70 032	1.70	1 (Ref.)	<0.001	1 (Ref.)	<0.001	1 (Ref.)	0.015
Acromegaly	1874	42	13 727	3.06	1.80 (1.27–2.56)		1.83 (1.29–2.60)		1.59 (1.09–2.31)	
Congestive heart failure										
Controls	9370	114	70 111	1.63	1 (Ref.)	<0.001	1 (Ref.)	<0.001	1 (Ref.)	0.025
Acromegaly	1874	43	13 829	3.11	1.92 (1.35–2.72)		1.95 (1.37–2.77)		1.54 (1.06–2.25)	
All-cause death										
Controls	9370	284	70 414	4.03	1 (Ref.)	<0.001	1 (Ref.)	<0.001	1 (Ref.)	0.040
Acromegaly	1874	88	13 949	6.31	1.57 (1.24–1.99)		1.59 (1.25–2.02)		1.31 (1.01–1.69)	

Model 1: adjusted by age and sex. Model 2: adjusted by age, sex, household income, place, Type 2 diabetes, hypertension, and dyslipidaemia.

dyslipidaemia [HR: 0.98, 95% confidence interval (CI): 0.69–1.39, $P = 0.907$; *Table 2*].

Myocardial infarction was identified in 14 (0.75%) patients with acromegaly and 66 (0.70%) controls during the mean follow-up period of 7.41 ± 3.24 years and 7.49 ± 3.21 years, respectively (*Table 2*). *Figure 1B* presents the results of Kaplan–Meier survival analysis for myocardial infarction. The incident rate of myocardial infarction was 1.01 per 1000 person-years in patients with acromegaly and 0.94 per 1000 person-years in controls (log-rank, $P = 0.813$). The risk for myocardial infarction in patients with acromegaly was not higher than that of controls in multivariable Cox proportional hazards regression modelling after adjusting for age, sex, household income, place, Type 2 diabetes, hypertension, and dyslipidaemia (HR: 0.75, 95% CI: 0.41–1.39, $P = 0.361$; *Table 2*).

Stroke was identified in 32 (1.78%) patients with acromegaly and 126 (1.35%) controls during the mean follow-up period of 7.37 ± 3.25 years and 7.47 ± 3.21 years, respectively (*Table 2*). *Figure 1C* presents the results of Kaplan–Meier survival analysis for stroke. The incident rate of stroke was 2.32 per 1000 person-years in patients with acromegaly and 1.80 per 1000 person-years in controls (log-rank, $P = 0.203$). The risk for stroke in patients with acromegaly was not higher than that of controls in multivariable Cox proportional hazards regression modelling after adjusting for age, sex, household income, place, Type 2 diabetes, hypertension, and dyslipidaemia (HR: 1.07, 95% CI: 0.71–1.62, $P = 0.750$; *Table 2*).

Acromegaly and atrial fibrillation

Atrial fibrillation was identified in 42 (2.24%) patients with acromegaly and 119 (1.27%) controls during the mean follow-up period of 7.32 ± 3.28 years and 7.47 ± 3.21 years, respectively. *Figure 1D* presents the results of Kaplan–Meier survival analysis for atrial fibrillation. The incident rate of atrial fibrillation in patients with acromegaly was significantly higher than in controls (3.06 per 1000 person-years vs. 1.70 per 1000 person-years; log-rank, $P < 0.001$). In multivariable Cox proportional hazards regression modelling, the risk of atrial fibrillation was significantly higher in patients with acromegaly than that in the control group (HR: 1.83; 95% CI: 1.29–2.60, $P < 0.001$; *Table 2*) after adjusting for age and sex and also after adjusting for age, sex, household income, place, Type 2 diabetes, hypertension, and dyslipidaemia (HR: 1.59; 95% CI: 1.09–2.31, $P = 0.015$; *Table 2*).

Acromegaly and congestive heart failure

Congestive heart failure was identified in 43 (2.30%) patients with acromegaly and 114 (1.22%) controls during the mean follow-up period of 7.38 ± 3.25 years and 7.48 ± 3.21 years, respectively. *Figure 1E* presents the results of Kaplan–Meier survival analysis for congestive heart failure. The incident rate of congestive heart failure in patients with acromegaly was significantly higher than that in controls (3.11 per 1000 person-years vs. 1.63 per 1000 person-years; log-rank, $P < 0.001$). In multivariable Cox proportional hazards regression modelling, the risk of congestive heart failure was significantly higher in patients with acromegaly than that in the control group (HR: 1.95; 95% CI: 1.35–2.77, $P < 0.001$; *Table 2*) after adjusting for age and sex and also after adjusting for age, sex, household income, place, Type 2 diabetes, hypertension, and dyslipidaemia (HR: 1.54; 95% CI: 1.06–2.25, $P = 0.025$; *Table 2*).

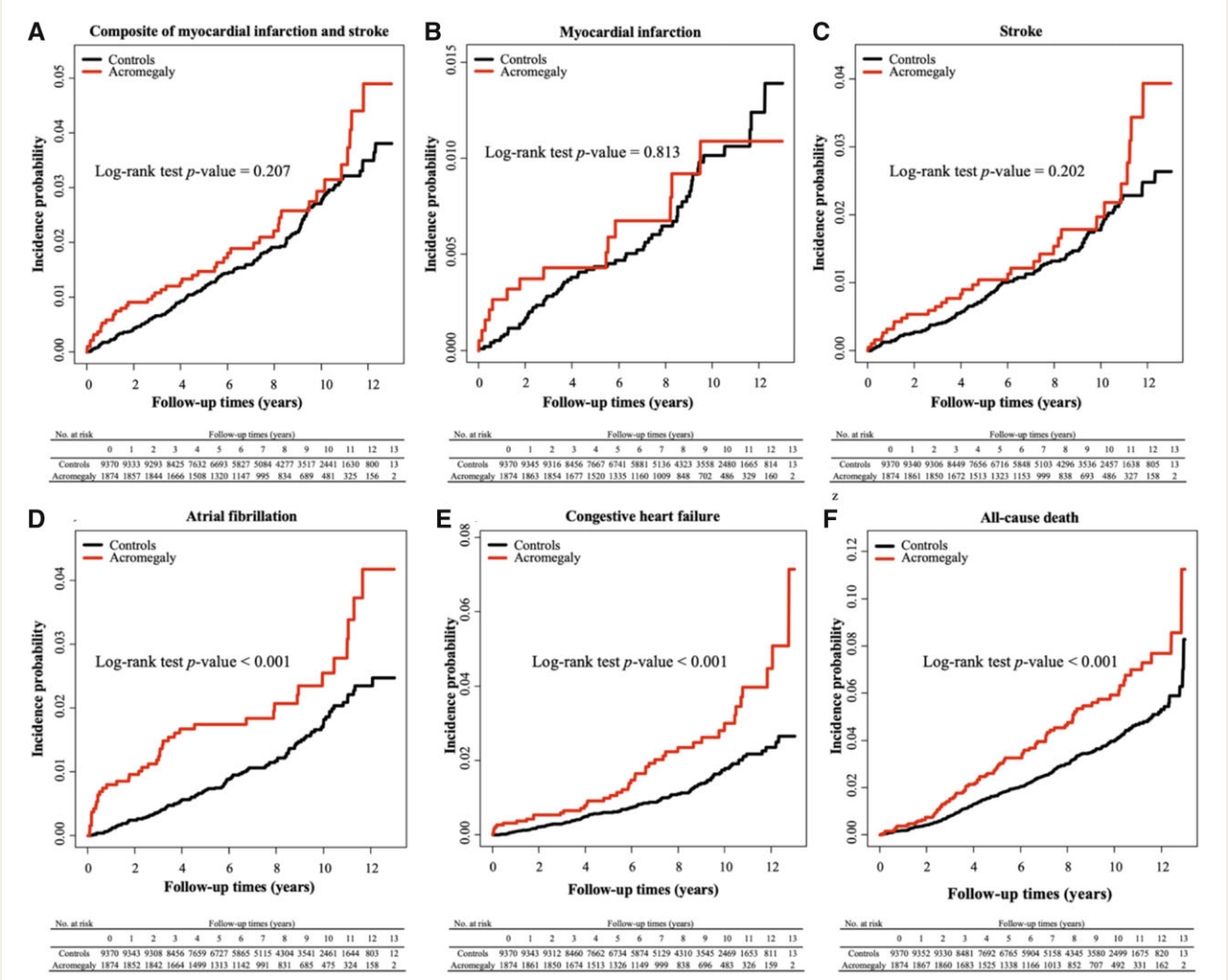

Figure 1 The cumulative incidence of outcomes based on Kaplan–Meier analysis. (*A*) Composite of myocardial infarction and stroke, (*B*) myocardial infarction, (*C*) stroke, (*D*) atrial fibrillation, (*E*) congestive heart failure, and (*F*) all-cause death by follow-up duration of acromegaly from the time of diagnosis and age- and sex-matched controls, during an average follow-up of 7.35 ± 3.27 and 7.44 ± 3.22 years, respectively. The *P*-value was calculated using the log-rank test.

Acromegaly and all-cause death

All-cause death was identified in 88 (4.70%) patients with acromegaly and 284 (3.03%) controls during the mean follow-up period of 7.44 ± 3.23 years and 7.51 ± 3.2 years, respectively. *Figure 1F* presents the results of Kaplan–Meier survival analysis for all-cause death. The incident rate of all-cause death in patients with acromegaly was significantly higher than that in controls (6.31 per 1000 person-years vs. 4.03 per 1000 person-years; log-rank, $P < 0.001$). For all-cause death, acromegaly accounted 36% of events. In multivariable Cox proportional hazards regression modelling, the risk of all-cause death was significantly higher in patients with acromegaly than that in the control group (HR: 1.59; 95% CI: 1.25–2.02, $P < 0.001$; *Table 2*) after adjusting for age and sex and also after adjusting for age, sex, household income, place, Type 2 diabetes, hypertension, and dyslipidaemia (HR: 1.31; 95% CI: 1.01–1.69, $P = 0.040$; *Table 2*).

Sensitivity analysis: longitudinal associations between acromegaly and cardiovascular disease

Figure 2 shows the risk for outcomes in patients with acromegaly compared with controls by observation period [entire study period, first 4 years of observation, and time lag over 4 years (excluding the first 4 years of observation)]. In multivariable Cox proportional hazards regression modelling with age and sex, the risk for composite of myocardial infarction and stroke was similar in patients with acromegaly compared with controls during the first 4 years of observation (HR: 1.41; 95% CI: 0.88–2.24, $P = 0.145$) and after excluding the first 4 years (HR: 1.05; 95% CI: 0.65–1.69, $P = 0.857$). After additional adjustment for Type 2 diabetes, hypertension, and dyslipidaemia, the risk for the composite outcome of myocardial infarction and stroke was not different between patients with acromegaly and controls

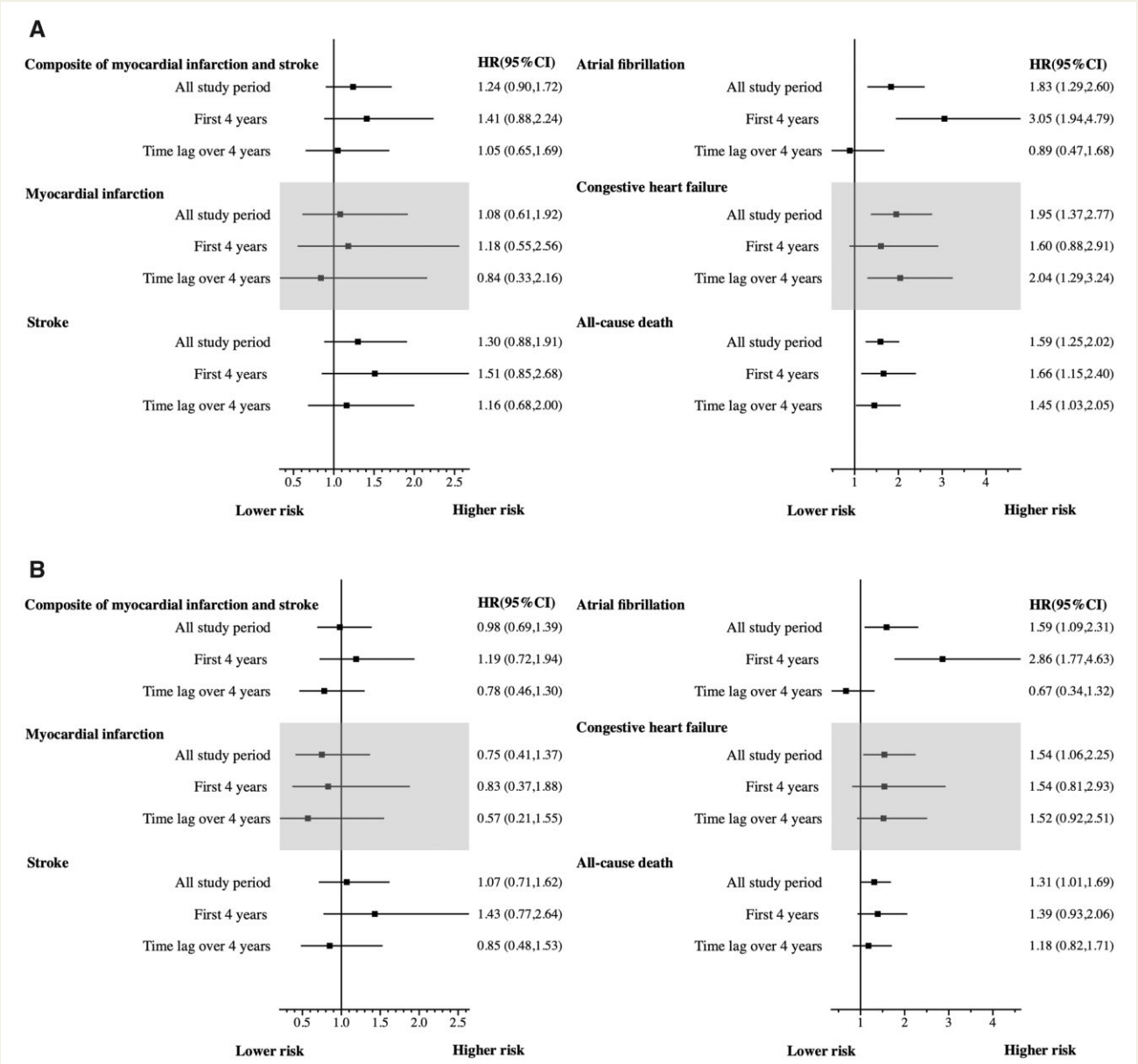

Figure 2 Hazard ratio for a composite of myocardial infarction and stroke, myocardial infarction, stroke, atrial fibrillation, congestive heart failure, and all-cause death in patients with acromegaly compared with controls by lag times adjusted by (*A*) age and sex and (*B*) age, sex, household income, place, Type 2 diabetes, hypertension, and dyslipidaemia.

during the first 4 years of observation ($P = 0.499$) or after excluding the first 4 years of observation ($P = 0.331$). The risk for myocardial infarction and stroke was similar to that of the composite of myocardial infarction and stroke (*Figure 2*).

In multivariable Cox proportional hazards regression modelling with age, sex, household income, place, Type 2 diabetes, hypertension, and dyslipidaemia, the risk for atrial fibrillation in patients with acromegaly was increased compared with controls during the first 4 years of observation (HR: 2.86; 95% CI: 1.77–4.63, $P < 0.001$), but was not different compared with controls after excluding the first 4 years of observation (HR: 0.67; 95% CI: 0.34–1.32, $P = 0.244$).

In multivariable Cox proportional hazards regression modelling with age and sex, the risk for congestive heart failure in patients with acromegaly compared with controls was similar in the entire study period (HR: 1.95; 95% CI: 1.37–2.77, $P < 0.001$), the first 4 years (HR: 1.60; 95% CI: 0.88–2.91, $P = 0.127$), and after excluding the first 4 years of observation (HR: 2.04; 95% CI: 1.29–3.24, $P = 0.003$). However, after adjusting for age, sex, household income, place, Type 2 diabetes, hypertension, and dyslipidaemia, the risk for congestive heart failure was attenuated in patients with acromegaly compared with controls after excluding the first 4 years of observation

(HR: 1.52; 95% CI: 0.92–2.51, $P = 0.104$) but not in the first 4 years (HR: 1.54; 95% CI: 0.81–2.93, $P = 0.188$).

In multivariable Cox proportional hazards regression modelling with age and sex, the risk for all-cause death in patients with acromegaly compared with controls was increased in the first 4 years (HR: 1.66; 95% CI: 1.15–2.40, $P = 0.007$) and after excluding the first 4 years of observation (HR: 1.45; 95% CI: 1.03–2.05, $P = 0.032$). The risk for all-cause death in patients with acromegaly compared with controls was also attenuated in the first 4 years (HR: 1.39; 95% CI: 0.93–2.06, $P = 0.105$) and excluding the first 4 years of observation (HR: 1.18; 95% CI: 0.82–1.71, $P = 0.369$) after adjusting for age, sex, household income, place, Type 2 diabetes, hypertension, and dyslipidaemia.

Discussion

In this nationwide, retrospective cohort study, we examined the association between acromegaly and the risk of myocardial infarction, stroke, atrial fibrillation, congestive heart failure, and all-cause death. During the approximate 7.4 years of follow-up, the risk for atrial fibrillation, congestive heart failure, and all-cause death were higher by 1.59-fold (95% CI: 1.09–2.31), 1.54-fold (95% CI: 1.06–2.25), and 1.31-fold (95% CI: 1.01–1.69), respectively, in patients with acromegaly compared with controls, and this finding was significant, irrespective of several confounders (age, sex, household incomes, place, Type 2 diabetes, hypertension, and dyslipidaemia). The higher risk for atrial fibrillation and the composite outcome of myocardial infarction and stroke in patients with acromegaly compared with controls was time-dependent and was observed only during the first 4 years of follow-up. However, higher risk for congestive heart failure and all-cause death in patients with acromegaly was not time-dependent, but was attenuated after adjusting for Type 2 diabetes, hypertension, and dyslipidaemia (*Graphical Abstract*). Although the results of an observational study should be interpreted with caution, our retrospective cohort model including 1874 patients with acromegaly provides new and important insight into the treatment of patients with acromegaly.

A meta-analysis of 18 studies including 4806 acromegaly patients from 1965 to 2008 indicated an average 10-year reduction in the life expectancy of acromegaly patients compared with the general population, with at least two-fold higher mortality rates due to cardiovascular, cerebrovascular, metabolic, and respiratory comorbidities.[18,19] However, according to a recent 20-year follow-up study, the rates of death from cardiovascular causes in patients with acromegaly gradually decreased from 44% during the first decade to 23% during the second decade.[20] In another recent retrospective study of acromegaly patients treated at specialized centres, the incidence of myocardial infarction and stroke in patients with acromegaly was similar to that of the general population. The authors suggested that the incidence of myocardial infarction and stroke in well-treated acromegaly patients does not differ from the general population.[21] Our nationwide study showed similar results. Although patients with acromegaly had high cardiovascular risk with a higher prevalence of diabetes, hypertension, and dyslipidaemia at baseline compared with the control group, the incidence of myocardial infarction and stroke in patients with acromegaly did not vary from that of the control group. A few studies have demonstrated how the cardiovascular effects of acromegaly may be mediated by other cardiovascular risk factors such as diabetes, hypertension, and dyslipidaemia. In a recent retrospective cohort study of patients with acromegaly, age (HR: 1.09, $P = 0.005$) and smoking status (HR: 5.95, $P = 0.01$) were predictors of cardiovascular events, while hypertension (HR: 1.33, $P = 0.64$) and diabetes (HR: 0.89, $P = 0.89$) were not in multivariate Cox regression analyses.[22] In our study of controls without acromegaly, Model 2, which adjusted for cardiovascular risk factors, showed lower risk for the composite outcome of myocardial infarction and stroke (HR: 0.98, 95% CI: 0.69–1.39, $P = 0.907$) compared with the unadjusted model (HR: 1.23, 95% CI: 0.89–1.71, $P = 0.207$, *Table 2*). This suggested that the cardiovascular effects of acromegaly are mainly mediated by diabetes, hypertension, and dyslipidaemia. Although glucose and lipid abnormalities are frequent in patients with acromegaly, most treatments for acromegaly improve insulin resistance and hyperinsulinaemia, as well as decreasing triglyceride levels, and increase HDL levels without modifying LDL-cholesterol levels.[23–25] Several studies showed that long-term control of acromegaly is associated with amelioration of hypertension.[26] This is consistent with our findings that HRs were decreased in lag time analysis, which indicated that appropriate treatment for acromegaly reduced the risk for myocardial infarction and stroke. Although mortality of patients with acromegaly was 1.31 times higher than that of controls, this finding weakened with lag time analysis and disappeared after adjusting for diabetes, hypertension, and dyslipidaemia (*Figure 2*). This was consistent with a recent systematic review and meta-analysis, which suggested that mortality in acromegaly can be normalized with biochemical control and has decreased over the last decade with increased use of somatostatin analogues as adjuvant therapy.[27]

Acromegaly is associated with a cardiomyopathy, characterized by biventricular hypertrophy, mainly involving the left ventricle in 80% of cases and consequent diastolic dysfunction in 58% of patients with active disease.[28] The progression to systolic dysfunction in acromegaly is generally uncommon (<3% of cases) and the presence of overt congestive heart failure is rare (ranging between 1% and 4% in patients with untreated and uncontrolled disease). In our study, congestive heart failure was identified in 2.30% of patients with acromegaly during the mean follow-up period of 7.38 ± 3.25 years. The risk for congestive heart failure in patients with acromegaly was nearly two-fold higher than that of the control group and remained significantly higher (by 1.5-fold) even after adjustment for Type 2 diabetes, hypertension, and dyslipidaemia. In lag time sensitivity analysis (*Figure 2*), the risk for congestive heart failure in patients with acromegaly compared with controls was not time-dependent with adjustment for age and sex, but was attenuated after adjusting for Type 2 diabetes, hypertension, and dyslipidaemia, which are known risk factors for congestive heart failure. Several studies reported that treatment for acromegaly, such as somatostatin analogues, GH receptor antagonist, and surgical treatment, can decrease left ventricular hypertrophy and improve diastolic dysfunction,[29–31] and these findings suggested that to prevent the development of congestive heart failure. However, long-term data for congestive heart failure in patients with acromegaly are scarce. Our study results suggest that other treatment strategies are needed, including more strict control for Type 2 diabetes, hypertension, and dyslipidaemia, to prevent the development of congestive heart failure in patients with acromegaly. Further prospective studies are also needed.

Arrhythmia has been less frequently studied in patients with acromegaly than structural heart changes. Few studies have provided evidence that patients with acromegaly are at high risk of arrhythmias, especially those with structural cardiac abnormalities. Kahaly *et al.*[32] reported that complex ventricular arrhythmias, but not supraventricular arrhythmias, were significantly more prevalent and more severe in patients with acromegaly (48%) than in controls (12%) on 24 h electrocardiogram Holter monitoring. However, Warszawski *et al.*[33] reported no clinically relevant arrhythmias on 24 h electrocardiogram Holter monitoring in treatment-naive acromegalics or in patients after 1 year of somatostatin analogue treatment. In our study, the risk of atrial fibrillation was 1.6 times higher in patients with acromegaly than in the control group, but these findings were not significant in sensitivity analysis with lag time. This indicates that the risk of atrial fibrillation might be ameliorated by treatment for acromegaly. A previous study reported that ~62% of patients with acromegaly were diagnosed with an enlarged left atrium,[34] and an enlarged left atrium increases the risk of arrhythmia, especially atrial fibrillation. Therefore, Popielarz-Grygalewicz *et al.*[34] suggested the need for periodic follow-up using 24 h electrocardiogram Holter monitoring, as these patients are predisposed to paroxysmal arrhythmia. We agree with this suggestion but suggest monitoring should be focused within the first 4 years after diagnosis. The incidence of atrial fibrillation increases with age in the general population.[35] We compared the association between acromegaly atrial fibrillation by tertiles of age at inclusion (see Supplementary material online, *Table S2*). The incidence of atrial fibrillation increased with age (<40 vs. 40–64 vs. ≥65 years old) in both patients with acromegaly (1.22 vs. 3.63 vs. 5.49 person-years) and controls (0.29 vs. 1.54 vs. 8.18 person-years). In multivariable Cox proportional hazards regression modelling, the risk for atrial fibrillation in older patients with acromegaly compared with older controls (HR: 0.63; 95% CI: 0.26–1.52) was significantly lower (*P* for interaction = 0.0194) than the risk for atrial fibrillation in younger patients with acromegaly (HR: 5.50, 95% CI: 1.68–18.05) compared with younger controls. These associations were more prominent during the first 4 years. This may be related to the previous observation that basal GH and IGF-1 levels and post glucose tolerance test GH nadir seem to be lower in elderly patients than in younger patients.[36]

The strengths of our study are that this study included a large number of patients with acromegaly ($n = 1874$) and age- and sex-matched case–controls ($n = 9370$). We also conducted fully adjusted analyses with all available confounding factors and subgroup analysis. However, this study also has some limitations. First, it had a retrospective observational design. Although the analyses were adjusted for most available demographic and clinical variables, some unidentified parameters could have affected the results. Nevertheless, acromegaly is a rare disease, and therefore a large prospective study might not be possible. Second, we defined acromegaly and outcomes using claims data; this may not be a completely accurate method for determining the number of cases. To overcome this problem, we defined acromegaly using a national registry system for rare incurable diseases and applied the definition of outcomes that had been validated in previous studies that used a Korean NHIS sample cohort.[37–39] Third, comorbidities such as diabetes, hypertension, and dyslipidaemia were defined using claims data without blood glucose, glycated haemoglobin, arterial blood pressure, and blood lipids levels, which were not available in our study data. To minimize bias, we applied a definition of diabetes, hypertension, and dyslipidaemia already validated in previous studies.[40–42] Fourth, there might be some difference in healthcare utilization between subjects with acromegaly and without acromegaly, which could cause reporting bias. To minimize this bias, we excluded patients who had the outcomes at baseline. Cardiovascular disease workup, electrocardiography, and echocardiography were not included in routine care of acromegaly;[43] thus, those workups were done based on new symptoms in both subjects with and without acromegaly. Fifth, this study was not a prospective study, and therefore causality cannot be determined. However, to minimize the possible effects of reverse causality, subjects with pre-existing conditions were excluded and lag time sensitivity analysis was done.

In conclusion, this nationwide, observational, retrospective cohort study of patients with acromegaly showed that the risk of myocardial infarction and stroke were not increased, but the risk of atrial fibrillation, congestive heart failure, and all-cause death were higher in patients with acromegaly compared with controls. These associations weakened with increased duration of treatment for acromegaly and adjustment for Type 2 diabetes, hypertension, and dyslipidaemia. Our results suggest that comprehensive treatment for acromegaly may minimize the risk of adverse events, and future studies should examine treatment strategies to further reduce adverse events in acromegaly.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Data availability

The data that support the findings of this study are available from the National Health Insurance Sharing Service (NHISS, https://nhiss.nhis.or.kr/). However, restrictions apply regarding the availability of the data, which were used with permission for the present study, and are therefore not publicly available. However, they may be made available through the corresponding author, upon reasonable request and with permission from the NHISS.

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