Table S1 Definitions of covariates and clinical outcomes

Diagnosis	ICD-10 codes	Additional diagnostic definitions
Covariates		
Hypertrophic cardiomyopathy	I42.1, I42.2	Admission or outpatient clinic ≥1
		Registration in the national registry for rare intractable diseases (RID code V127)
Atrial fibrillation	I48	Admission or outpatient clinic ≥1
Chronic obstructive pulmonary disease	J41-44	Admission or outpatient clinic ≥1
End-stage renal disease	N18.5, Z49	Dialysis ≥2
		Procedure codes: O7011-7020 (Hemodialysis), O7017, O7075 (Peritoneal dialysis)
Dyslipidemia	E78	Admission or outpatient clinic ≥1, and prescription of lipid-lowering medication (statin, ezetimibe, fenofibrate)
Components of CHA2DS2-VASc score		
Hypertension	I10-I13, I15	Admission ≥1 or outpatient clinic ≥2, and prescription of anti-hypertensive drug (thiazide, loop diuretics, aldosterone antagonist, alpha-/beta-blocker, calcium-channel blocker, angiotensin-converting enzyme inhibitor, angiotensin II receptor blocker)
Diabetes mellitus	E11-E14	Admission ≥1 or outpatient clinic ≥2, and prescription of anti-diabetic drugs (sulfonylureas, metformin, meglitinides, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, α-glucosidase inhibitors or insulin)
Ischemic stroke	I63, I64	Admission or outpatient clinic ≥1
Transient ischemic attack	G45.8, G45.9	Admission or outpatient clinic ≥1
Arterial thromboembolism	I74	Admission or outpatient clinic ≥1
Heart failure	I50	Admission or outpatient clinic ≥1
Vascular disease		
Prior myocardial infarction	I21, I22	Admission or outpatient clinic ≥1
Peripheral artery disease	I70, I73	Admission ≥1 or outpatient clinic ≥2
Outcomes		
Ischemic stroke	I63, I64	Admission ≥1 and claims for brain imaging (CT or MRI) ≥1
		(Procedure codes) HA441, HA451, HA461, HA851 (Brain CT); HE101, HE201, HE301, HE401, HE501 (Brain MRI)

Table S2 Incidence rate and risk for stroke by CHA$_2$DS$_2$-VASc scores in hypertrophic cardiomyopathy patients with and without atrial fibrillation (AF)

CHA$_2$DS$_2$-VASc score	Non-AF (n=7,180)				AF (n=1,169)				AF not on anticoagulation (n=569)			
	N	Event	IR[†]	HR (95% CI)	N	Event	IR[†]	HR (95% CI)	N	Event	IR[†]	HR (95% CI)
0	825	20	0.86	1 (ref.)	53	4	3.37	1 (ref.)	36	2	2.50	1 (ref.)
1	1,980	60	1.21	1.38 (0.83–2.30)	210	14	2.94	0.86 (0.28–2.62)	126	8	2.75	1.07 (0.23–5.03)
2	1,838	94	2.10	2.41 (1.49–3.90)	299	29	4.23	1.25 (0.44–3.55)	161	17	4.81	1.80 (0.42–7.79)
3	1,260	100	3.26	3.73 (2.31–6.03)	252	38	6.71	1.96 (0.70–5.50)	100	15	6.76	2.55 (0.58–11.18)
4	747	88	4.69	5.40 (3.32–8.78)	195	28	6.53	1.91 (0.67–5.46)	79	10	5.17	1.99 (0.44–9.12)
5	364	60	6.52	7.54 (4.55–12.51)	98	17	8.39	2.44 (0.82–7.25)	44	7	8.01	3.06 (0.64–14.7)
6–9	166	62	18.4	21.38 (12.9–35.4)	62	22	19.6	5.74 (1.97–16.7)	23	8	21.2	7.62 (1.61–36.0)

[†] Incidence rate: per 100 person-years.

Table S3 Comorbidities as risk factors for stroke in hypertrophic cardiomyopathy patients with and without atrial fibrillation (AF)

	Non-AF (n=7,180)				AF (n=1,169)			
	IR[†]		Univariate HR	Adjusted HR[‡]	IR[†]		Univariate HR	Adjusted HR[‡]
	(-) (ref)	(+)			(-) (ref)	(+)		
Age ≥65	1.40	4.83	3.46 (2.86–4.12)	2.93 (2.37–3.63)	4.05	7.46	1.84 (1.31–2.58)	1.73 (1.21–2.51)
Female sex	2.24	3.65	1.65 (1.38–1.97)	0.96 (0.76–1.22)	5.40	6.85	1.27 (0.92–1.77)	1.00 (0.66–1.52)
Hypertension	2.09	3.00	1.43 (1.17–1.76)	1.10 (0.89–1.36)	6.14	5.76	0.94 (0.67–1.34)	0.92 (0.64–1.32)
Diabetes mellitus	2.51	3.50	1.39 (1.13–1.71)	1.15 (0.93–1.42)	6.39	4.02	0.63 (0.41–0.99)	0.55 (0.35–0.87)
Dyslipidemia	2.40	3.01	1.25 (1.04–1.49)	1.06 (0.89–1.28)	5.80	5.96	1.03 (0.75–1.42)	1.07 (0.77–1.49)
Heart failure	2.65	5.26	1.98 (1.18–3.31)	1.41 (0.83–2.38)	5.63	10.2	1.82 (1.05–3.15)	2.05 (1.17–3.60)
Prior MI	2.68	3.84	1.43 (0.74–2.77)	1.28 (0.66–2.49)	5.95	2.98	0.51 (0.13–2.04)	0.42 (0.10–1.72)
PAD	2.49	4.32	1.75 (1.38–2.21)	1.30 (1.02–1.64)	5.65	7.32	1.30 (0.84–1.99)	1.17 (0.75–1.81)
COPD	2.48	4.80	1.72 (1.37–2.16)	1.21 (0.96–1.53)	5.79	6.23	1.07 (0.71–1.61)	0.91 (0.60–1.38)
ESRD	2.69	3.04	1.15 (0.29–4.59)	1.43 (0.35–5.81)	5.85	9.77	1.63 (0.23–11.7)	1.31 (0.17–9.88)

[†]Incidence rate: per 100 person-years. [‡]Adjusted for age, sex, comorbidities (hypertension, diabetes mellitus, dyslipidemia, heart failure, prior MI, PAD, COPD, ESRD), body mass index, creatinine clearance, smoking, drinking, exercise, presence of oral anticoagulation. HR, hazard ratio; MI, myocardial infarction; PAD, peripheral artery disease; COPD, chronic obstructive pulmonary disease; ESRD, end-stage renal disease.

Table S4 Health checkup variables as risk factors for stroke in hypertrophic cardiomyopathy patients with and without atrial fibrillation

	Non-AF (n=7,180)			AF (n=1,169)		
	IR[†]	Univariate HR	Adjusted HR[‡]	IR[†]	Univariate HR	Adjusted HR[‡]
Body mass index						
<25	3.14	1 (ref)	1 (ref)	6.44	1 (ref)	1 (ref)
≥25	2.25	0.72 (0.60–0.86)	0.80 (0.67–0.96)	5.24	0.81 (0.56–1.12)	0.88 (0.63–1.23)
Waist circumference						
Q1	2.65	1 (ref)	1 (ref)	6.68	1 (ref)	1 (ref)
Q2	2.96	1.11 (0.87–1.41)	1.22 (0.94–1.60)	5.49	0.81 (0.52–1.26)	1.05 (0.64–1.73)
Q3	2.77	1.04 (0.81–1.35)	1.27 (0.92–1.74)	5.09	0.76 (0.48–1.21)	0.97 (0.54–1.73)
Q4	2.40	0.90 (0.70–1.17)	1.14 (0.78–1.66)	6.11	0.91 (0.60–1.39)	1.41 (0.71–2.78)
SBP/DBP						
<120/<80	2.58	1 (ref)	1 (ref)	5.54	1 (ref)	1 (ref)
120–129/80–84	2.89	1.13 (0.91–1.39)	1.11 (0.90–1.38)	6.47	1.16 (0.79–1.72)	1.18 (0.79–1.76)
130–139/85–89	2.45	0.96 (0.68–1.36)	0.96 (0.68–1.37)	5.67	1.02 (0.57–1.83)	1.23 (0.68–2.22)
140–159/90–99	3.13	1.24 (0.89–1.72)	1.07 (0.76–1.49)	6.09	1.09 (0.59–2.05)	1.18 (0.62–2.24)
≥160/≥100	3.20	1.31 (0.67–2.54)	1.48 (0.76–2.90)	22.0	3.97 (1.26–12.6)	3.82 (1.17–12.5)
Fasting glucose						
<100	2.60	1 (ref)	1 (ref)	6.03	1 (ref)	1 (ref)
100–125	2.60	0.99 (0.82–1.21)	0.91 (0.74–1.12)	6.11	1.02 (0.72–1.43)	1.09 (0.77–1.55)
≥126	3.43	1.31 (1.00–1.72)	1.07 (0.72–1.59)	4.38	0.72 (0.40–1.29)	1.35 (0.57–3.19)
Total cholesterol						
Q1	3.52	1 (ref)	1 (ref)	5.92	1 (ref)	1 (ref)
Q2	2.78	0.80 (0.63–1.02)	0.89 (0.69–1.14)	4.7	0.81 (0.52–1.26)	0.84 (0.53–1.34)
Q3	1.98	0.57 (0.44–0.74)	0.71 (0.54–0.93)	6.97	1.18 (0.78–1.80)	1.28 (0.82–1.99)
Q4	2.64	0.76 (0.60–0.97)	0.93 (0.73–1.19)	6.06	1.04 (0.66–1.64)	1.11 (0.69–1.80)
LDL-C						
Q1	3.23	1 (ref)	1 (ref)	4.81	1 (ref)	1 (ref)
Q2	3.02	0.94 (0.74–1.20)	1.01 (0.79–1.28)	5.52	1.16 (0.74–1.83)	1.14 (0.72–1.81)
Q3	1.94	0.61 (0.47–0.80)	0.71 (0.53–0.93)	7.35	1.53 (0.97–2.40)	1.73 (1.07–2.79)
Q4	2.65	0.84 (0.66–1.07)	1.03 (0.80–1.32)	6.02	1.27 (0.78–2.09)	1.29 (0.77–2.15)
HDL-C						
Q1	2.72	0.93 (0.73–1.19)	0.97 (0.75–1.25)	5.64	1.06 (0.67–1.68)	1.07 (0.67–1.72)
Q2	2.66	0.91 (0.71–1.18)	0.97 (0.75–1.25)	5.60	1.06 (0.66–1.70)	1.10 (0.68–1.78)
Q3	2.48	0.85 (0.66–1.10)	0.88 (0.68–1.14)	7.02	1.32 (0.84–2.06)	1.33 (0.85–2.10)
Q4	2.90	1 (ref)	1 (ref)	5.30	1 (ref)	1 (ref)
Triglycerides						
Q1	2.41	1 (ref)	1 (ref)	6.87	1 (ref)	1 (ref)
Q2	3.06	1.28 (0.99–1.66)	1.24 (0.96–1.61)	5.90	0.86 (0.57–1.29)	0.88 (0.58–1.34)
Q3	2.76	1.16 (0.89–1.50)	1.15 (0.88–1.50)	5.20	0.77 (0.49–1.19)	0.82 (0.52–1.28)
Q4	2.54	1.06 (0.82–1.38)	1.16 (0.89–1.53)	5.21	0.77 (0.48–1.24)	0.83 (0.51–1.36)
Hemoglobin						
Q1	3.62	1 (ref)	1 (ref)	7.34	1 (ref)	1 (ref)
Q2	2.87	0.79 (0.63–0.99)	1.08 (0.85–1.37)	5.28	0.72 (0.47–1.10)	0.89 (0.57–1.39)
Q3	1.99	0.54 (0.42–0.70)	1.01 (0.75–1.36)	5.37	0.73 (0.47–1.14)	1.03 (0.62–1.69)
Q4	2.24	0.61 (0.47–0.78)	1.35 (0.99–1.84)	5.32	0.72 (0.47–1.13)	1.07 (0.63–1.82)
CrCl						
<60	4.63	2.98 (1.60–2.43)	1.26 (1.01–1.57)	7.03	1.29 (0.91–1.83)	1.03 (0.72–1.50)
≥60	2.38	1 (ref)	1 (ref)	5.48	1 (ref)	1 (ref)
ALT						
Q1	3.39	1 (ref)	1 (ref)	6.12	1 (ref)	1 (ref)
Q2	2.70	0.80 (0.63–1.01)	0.94 (0.74–1.20)	5.86	0.96 (0.62–1.47)	1.05 (0.68–1.63)
Q3	2.48	0.73 (0.57–0.92)	0.98 (0.76–1.26)	6.10	1.00 (0.64–1.54)	1.20 (0.76–1.89)
Q4	2.17	0.63 (0.49–0.82)	0.96 (0.74–1.27)	5.35	0.87 (0.55–1.40)	0.10 (0.68–1.78)
AST						
Q1	2.50	1 (ref)	1 (ref)	5.24	1 (ref)	1 (ref)
Q2	2.83	1.12 (0.88–1.44)	1.15 (0.90–1.47)	4.64	0.89 (0.54–1.46)	0.88 (0.53–1.47)
Q3	2.39	0.95 (0.73–1.23)	1.01 (0.77–1.31)	6.79	1.28 (0.80–2.05)	1.27 (0.79–2.06)
Q4	3.07	1.21 (0.94–1.56)	1.37 (1.06–1.78)	6.73	1.27 (0.80–2.02)	1.33 (0.83–2.13)
GGT						
Q1	2.79	1 (ref)	1 (ref)	4.22	1 (ref)	1 (ref)
Q2	2.78	1.00 (0.78–1.27)	1.23 (0.96–1.57)	5.23	1.23 (0.69–2.19)	1.27 (0.71–2.30)
Q3	2.18	0.78 (0.60–1.02)	1.14 (0.86–1.50)	5.24	1.23 (0.71–2.13)	1.46 (0.82–2.59)
Q4	3.03	1.08 (0.85–1.38)	1.78 (1.35–2.35)	7.68	1.79 (1.08–2.99)	2.26 (1.30–3.93)
Smoking						
Non-smoker	3.34	1 (ref)	1 (ref)	6.52	1 (ref)	1 (ref)
Ex-smoker	1.93	0.57 (0.45–0.72)	0.71 (0.54–0.94)	5.46	0.83 (0.58–1.20)	1.04 (0.67–1.62)
Current smoker	2.08	0.63 (0.49–0.80)	0.96 (0.72–1.27)	4.37	0.68 (0.41–1.14)	0.90 (0.50–1.59)
Drinking						
Non-drinker	3.23	1 (ref)	1 (ref)	6.29	1 (ref)	1 (ref)
Mild drinker	1.91	0.59 (0.48–0.72)	1.00 (0.79–1.27)	4.84	0.76 (0.52–1.11)	0.99 (0.65–1.52)
Heavy drinker	2.38	0.74 (0.50–1.09)	1.39 (0.91–2.11)	5.81	0.89 (0.39–2.03)	1.33 (0.57–3.13)
Regular exercise						
No	3.30	1 (ref)	1 (ref)	6.58	1 (ref)	1 (ref)
Yes	2.08	0.63 (0.52–0.75)	0.84 (0.69–1.01)	4.95	0.85 (0.54–1.04)	0.79 (0.56–1.11)

[†]Incidence rate: per 100 person-years. [‡]Adjusted for age, sex, comorbidities (hypertension, diabetes mellitus, dyslipidemia, heart failure, prior myocardial infarction, peripheral artery disease, chronic obstructive pulmonary disease, end-stage renal disease), body mass index, creatinine clearance, smoking, drinking, exercise, presence of oral anticoagulation. HR, hazard ratio; CI, confidence interval; Q1, lowest quartile; Q4, highest quartile; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; CrCl, creatinine clearance; ALT, alanine transaminase; AST, aspartate transaminase; GGT, gamma-glutamyltransferase.

Table S5 Quartile ranges

	Q1	Q2	Q3	Q4
Waist circumference	≤80	81–86	87–91	≥92
Total cholesterol	≤153	154–178	179–205	≥206
LDL-C	≤78	79–101	102–126	≥127
HDL-C	≤42	43–49	50–58	≥59
Triglycerides	≤83	84–114	115–162	≥163
Hemoglobin	≤13.3	13.4–14.5	14.6–15.5	≥15.6
ALT	≤17	18–23	24–33	≥34
AST	≤21	22–26	27–33	≥34
GGT	≤20	21–31	32–52	≥53

LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; ALT, alanine transaminase; AST, aspartate transaminase; GGT, gamma-glutamyltransferase.
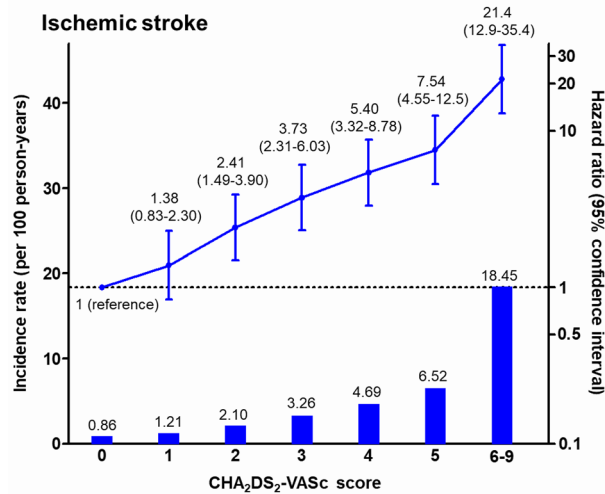

Figure S1 Performance of the CHA2DS2-VASc score for predicting stroke in hypertrophic cardiomyopathy patients without atrial fibrillation. Incidence rates (per 100 person-years) of stroke for each CHA2DS2-VASc scores are shown in bar graphs at the bottom with scales on the left. Hazard ratios with 95% confidence intervals representing the risk of stroke for each CHA2DS2-VASc scores are shown in line graphs with scales (base 10 logarithmic) on the right, with a dotted line at 1.