Appendix S1

MATERIALS AND METHODS

Data sources and study population

Study approval was obtained from the Danish Data Protection Agency (ref. 2007-58-0015, int. ref. GEH-2014-018, I-Suite 02736). Approval from an ethics committee is not required for register studies in Denmark. The study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations (7).

The study obtained information from the nationwide Danish Civil Registration System on individuals residing in Denmark. The Danish Register of Medicinal Products Statistics has recorded all pharmacy-dispensed prescriptions by individual identity number. The National Patient Registry contains individual-level information on all hospitalizations, including discharge diagnosis codes using the International Classification of Diseases (ICD), versions 8 and 10. Hospital procedures, including hospital-based pharmacological treatment, are coded in the register as treatment procedure codes. Information on tax-reported household income is recorded by Statistics Denmark, and information on age, sex, vital- and migration status are available from the Civil Registration System. All deaths and causes of deaths are registered in the National Causes of Death Registry using ICD-10 codes.

We identified all patients aged 18 years or older with a first-time (inpatient or outpatient) primary diagnosis of CU (ICD-10 codes L508A and L508B) or CSU (ICD-10 codes L5002A, L5002B, L504, L505, L506, L508C, L508E, or L563) between 1 January 1997 and 31 December 2012. The index date for cases was the date of first diagnosis, and each patient was matched (on age, sex, and calendar time) with 30 controls from the general population. Index date for controls was the index date for the corresponding cases, and the cohort was followed until migration, death from any cause, or the occurrence of an endpoint, whichever came first. A detailed study flow chart is available in Fig. S1[1]. The primary endpoints were a diagnosis of MI (I21–I22), ischaemic stroke (I63–I64), CV death (I00–I99), and MACE, respectively. The identification of MI and ischaemic stroke has been validated previously in the National Patient Registry (8, 9).

Covariates

Baseline treatment up to 6 months before study inclusion was defined for the following drugs: azathioprine, cholesterol-lowering drugs, cyclosporine, methotrexate, montelukast, and omalizumab, respectively. Baseline comorbidity was assessed up to 5 years prior to study inclusion for the following diagnoses: alcohol abuse, cardiovascular disease, diabetes, and hypertension, respectively. Diabetes was defined by either a hospital diagnosis, or use of glucose-lowering drugs. Collection of data on hypertension, smoking and alcohol abuse have been described in detail elsewhere (10–12). Previous cardiovascular disease was defined as the presence of at least one of the following diagnoses or treatment procedures: coronary artery bypass graft, percutaneous coronary intervention, percutaneous transluminal coronary angioplasty, MI, ischaemic heart disease, peripheral vascular disease, ischaemic stroke, thromboembolism, and transient ischaemic attack, respectively. We calculated an index of socioeconomic status (standardized by age) between 0 (lowest) and 4 (highest), based on the average gross annual income during a 5-year period before study inclusion.

Statistical analysis

Baseline characteristics were described using means and standard deviations for continuous variables, and frequencies and percentages for categorical variables. Incidence rates were summarized per 1,000 person-years, and Cox regression analyses were performed to estimate crude and fully adjusted (adjusted for age [continuous], sex [m/f], socio-economic status [categorical; 2=reference], medication, and comorbidity [0/1]) hazard ratios (HRs), respectively. Information was continually updated during the follow-up period. Model assumptions were tested and found to be valid. All statistical tests were conducted using a level of significance of 0.05 and results reported with 95% confidence intervals (CIs) where applicable. All analyses were performed using SAS statistical software version 9.4 (SAS Institute Inc. Cary, NC, USA) and STATA software version 13.0 (StataCorp, College Station, TX, USA). Since presentation of data on groups of fewer than 3 individuals from the present data sources is not permitted, results of 1 or 2 events or individuals are shown as <3.

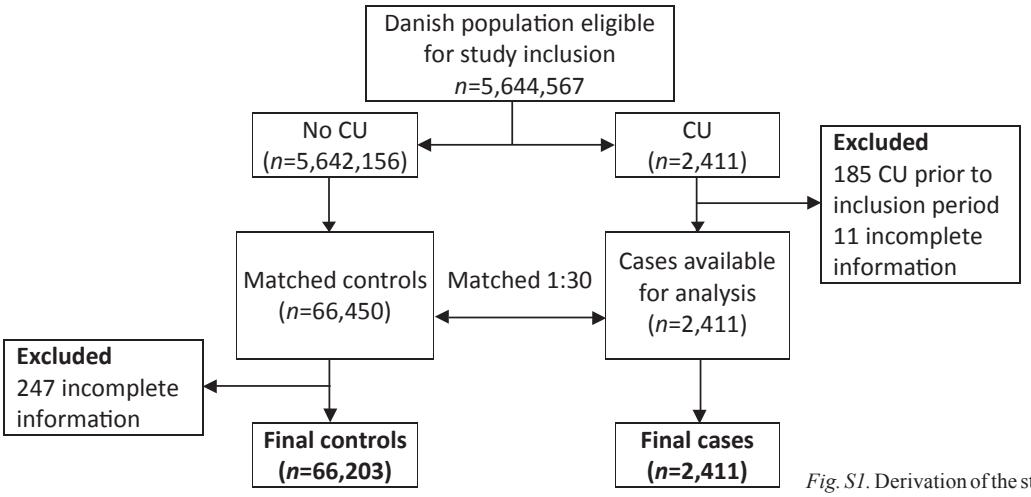

Fig. S1. Derivation of the study sample. CU: chronic urticaria.

Supplementary material to article by A. Egeberg et al. "Cardiovascular Risk is not Increased in Patients with Chronic Urticaria: A Retrospective Population-based Cohort Study"

Table SI. Baseline characteristics

	Chronic urticaria		Inducible urticaria	
	Controls ($n = 66,203$)	Cases ($n = 2215$)	Controls ($n = 28,497$)	Cases ($n = 977$)
Age	43.8 (14.5)	43.8 (14.5)	41.1 (14.3)	41.2 (14.2)
Mean (SD)	42.6 (69.7)	42.6 (69.7)	40.5 (66.1)	41.0 (66.1)
Median (range)	33.1–53.7	33.1–53.7	29.6–51.1	29.9–51.1
IQR				
Women, *n* (%)	45,920 (69.4)	1536 (69.4)	16,834 (59.1)	586 (60.0)
Men, *n* (%)	20,283 (30.6)	679 (30.6)	11,663 (40.9)	391 (40.0)
Socioeconomic status, mean (SD)	2.0 (1.4)	2.0 (1.4)	2.0 (1.4)	2.1 (1.4)
Smoking, *n* (%)	5362 (8.1)	271 (12.2)	2602 (9.1)	114 (11.7)
Comorbidity, *n* (%)				
Alcohol abuse	831 (1.3)	26 (1.2)	433 (1.5)	26 (2.7)
Cardiovascular disease	3207 (4.8)	158 (7.1)	1140 (4.0)	62 (6.4)
Diabetes	1639 (2.5)	71 (3.2)	654 (2.3)	32 (3.3)
Hypertension	4778 (7.2)	180 (8.1)	1355 (4.8)	71 (7.3)
Medication, *n* (%)				
Antihistamines	2014 (3.0)	1599 (72.2)	683 (2.8)	326 (40.5)
Azathioprine	302 (0.5)	50 (2.3)	97 (0.3)	11 (1.1)
Cholesterol-lowering drugs	3422 (5.2)	119 (5.4)	821 (2.9)	24 (2.5)
Cyclosporine	5 (0.0)	8 (0.4)	3 (0.0)	3 (0.3)
Methotrexate	203 (0.3)	8 (0.4)	63 (0.2)	3 (0.3)
Montelukast	166 (0.3)	33 (1.5)	57 (0.2)	15 (1.5)
Omalizumab	0 (0.0)	0 (0.0)	0 (0.0)	< 3 (not shown)

SD: standard deviation; IQR: interquartile range.

Table SII. Follow-up time, number of events, incidence rates, and hazard ratios (HR) of myocardial infarction, ischaemic stroke, cardiovascular death, and major adverse cardiovascular events, respectively

	Chronic urticaria		Inducible urticaria	
	Controls	Cases	Controls	Cases
Myocardial infarction				
Follow-up time, years	385,254	13,102	184,850	6,286
Number of events	568	25	223	9
Incidence rate/1,000 person-years (95% confidence interval)	1.47 (1.36–1.60)	1.91 (1.29–2.82)	1.21 (1.06–1.38)	1.43 (0.75–2.75)
Unadjusted HR (95% confidence interval)	1.29 (0.87–1.93, $p=0.21$)		1.19 (0.61–2.31, $p=0.62$)	
Adjusted HR (95% confidence interval, p-value)	1.18 (0.79–1.76, $p=0.42$)		1.07 (0.55–2.08, $p=0.85$)	
Ischaemic stroke				
Follow-up time, years	384,578	13,059	184,784	6,282
Number of events	721	27	253	7
Incidence rate/1,000 person-years (95% confidence interval)	1.87 (1.74–2.02)	2.07 (1.42–3.01)	1.37 (1.21–1.55)	1.11 (0.53–2.34)
Unadjusted HR (95% confidence interval)	1.10 (0.75–1.62, $p=0.62$)		0.81 (0.38–1.72, $p=0.59$)	
Adjusted HR (95% confidence interval, p-value)	1.03 (0.70–1.52, $p=0.88$)		0.80 (0.38–1.70, $p=0.57$)	
Cardiovascular death				
Follow-up time, years	386,965	13,152	185,666	6,308
Number of events	526	13	153	4
Incidence rate/1,000 person-years (95% confidence interval)	1.36 (1.25–1.48)	1.00 (0.57–1.70)	0.82 (0.70–0.97)	0.63 (0.24–1.69)
Unadjusted HR (95% confidence interval)	0.73 (0.42–1.26, $p=0.26$)		0.77 (0.28–2.07, $p=0.60$)	
Adjusted HR (95% confidence interval, p-value)	0.67 (0.39–1.17, $p=0.16$)		0.63 (0.23–1.72, $p=0.37$)	
Major adverse cardiovascular events				
Follow-up time, years	382,956	13,013	183,999	6,260
Number of events	1.514	57	543	16
Incidence rate/1,000 person-years (95% confidence interval)	3.95 (3.76–4.16)	4.38 (3.38–5.68)	2.95 (2.71–3.21)	2.56 (1.57–4.17)
Unadjusted HR (95% confidence interval)	1.11 (0.86–1.44, $p=0.45$)		0.87 (0.53–1.42, $p=0.57$)	
Adjusted HR (95% confidence interval, p-value)	1.09 (0.83–1.42, $p=0.54$)		0.76 (0.46–1.25, $p=0.27$)	