

Nationwide cohort study of the leukotriene receptor antagonist montelukast and incident or recurrent cardiovascular disease

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Background: The leukotriene pathway has been associated with an increased cardiovascular risk. However, the effects of the antileukotriene treatment used in asthmatic patients on cardiovascular outcomes have remained largely unexplored. **Objective:** We sought to examine a potential protective role of the leukotriene receptor antagonist montelukast on future risk of incident and recurrent myocardial infarction and ischemic stroke.

Methods: A nationwide population-based cohort of approximately 7 million persons integrating data from the Prescribed Drug, Patient, Cause of Death, Income, Educational, and Emigration Registers was followed from July 1, 2005, to December 31, 2008. Analyses were performed in the whole population after exclusion of subjects with a prior cardiovascular diagnosis (incident events; sample size, $n = 6,910,923$ for myocardial infarction and $n = 6,932,578$ for stroke) and in subjects with a prior diagnosis (recurrent events; $n = 153,937$ and $n = 132,291$ for stroke and myocardial infarction, respectively).

Results: Cox proportional hazard ratios (HRs) did not reveal an association of montelukast use with incident events. In contrast to these findings, montelukast use was associated with a lower risk for recurrent stroke (HR, 0.62; 95% CI, 0.38-0.99) accounting for age, sex, education level, and yearly income. Adjusting the latter finding also for respiratory and cardiovascular medications and diagnoses revealed similar point estimates (HR, 0.62; 95% CI, 0.39-1.0). *Post hoc* analyses revealed a significant association of montelukast use with a lower risk for recurrent myocardial infarction in male subjects (HR, 0.65; 95% CI, 0.43-0.99).

Conclusion: These data provide a first indication for a potential role of the antiasthma drug montelukast for secondary prevention of cardiovascular disease. (J Allergy Clin Immunol 2012;■■■:■■■-■■■.)

Key words: Atherosclerosis, inflammation, myocardial infarction, pharmacoepidemiology, stroke

Inflammation is common feature of several chronic diseases, such as asthma and atherosclerosis. Both these conditions are associated with a systemic inflammatory response measurable based on increases in low-grade C-reactive protein levels.^{1,2} Although lipid-lowering drugs of the statin class can decrease the systemic inflammation associated with atherosclerosis,¹ there is presently no specific anti-inflammatory treatment to decrease cardiovascular risk.

Cysteinyl leukotrienes (CysLTs) are important inflammatory mediators initially recognized as potent bronchoconstrictors.³ Antagonists of the leukotriene CysLT₁ receptor subtype are used as a treatment for asthma.⁴ In addition, CysLTs induce leukocyte recruitment and activation,⁵ and asthmatic patients treated with the leukotriene receptor antagonist (LTRA) montelukast display decreased C-reactive protein levels compared with those seen in placebo-treated patients.² In addition to asthmatic airways, the atherosclerotic lesion is also a site of local CysLT biosynthesis and leukotriene receptor expression.⁶ Furthermore, experimental studies have shown that LTRAs inhibit atherosclerosis development, reduce intimal hyperplasia after vascular injury, and exert protective effects after cerebral ischemia and reperfusion.⁷ Finally, genetic variants within the leukotriene-synthesizing pathway are associated with an increased risk of stroke and myocardial infarction.⁸

Taken together, these observations indicate that leukotrienes might have additional pathophysiologic roles beyond their actions in asthma and that LTRAs potentially could inhibit the inflammatory response associated with atherosclerosis. Clinical trials have been initiated to evaluate the effects of antileukotrienes on biomarkers and atherosclerotic morphology in patients with coronary and carotid atherosclerosis.^{9,10} However, no previous study has evaluated the effects of the antileukotriene drugs used in asthmatic patients on cardiovascular outcome. Therefore the aim of the present study was to establish the effects of montelukast treatment on the incidence and recurrence of either myocardial infarction or ischemic stroke. To this end, a nationwide population-based cohort of approximately 7 million persons with data on dispensed drugs, hospital diagnosis, and causes of death was used to monitor the associations between montelukast exposure and cardiovascular events.

METHODS

Population

The cohort consisted of all Swedish residents older than 18 years on July 1, 2005, identified through their unique personal identification number. The

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Abbreviations used

ACE: Angiotensin-converting enzyme
 ATC: Anatomical Therapeutic Chemical
 COPD: Chronic obstructive pulmonary disease
 CysLT: Cysteinyl leukotriene
 HR: Hazard ratio
 ICD: International Classification of Diseases
 LTRA: Leukotriene receptor antagonist

follow-up started July 1, 2005, and the end of follow-up was December 31, 2008, or the first occurrence of the following: the respective cardiovascular event (as defined below), emigration from Sweden, or death. Data were collected from the following national registries: the Swedish Prescribed Drug Register, Patient Register, Cause of Death Register, Educational and Income Registers, and the Registry of Emigrations and Immigrations, maintained at the National Board of Health and Welfare (<http://www.socialstyrelsen.se>) and Statistics Sweden (<http://www.scb.se>). The data were analyzed anonymously, and the investigators did not have access to the identities of the subjects. The study was approved by the Ethics Committee of Karolinska Institutet, Stockholm, Sweden.

According to the *a priori* analysis plan outlined in Fig 1, the present study addressed the associations of montelukast use with the following 4 outcomes: (1) incident myocardial infarction in subjects without a prior myocardial infarction, (2) recurrent myocardial infarction in subjects with a prior myocardial infarction diagnosis, (3) incident ischemic stroke in subjects without a prior ischemic stroke, and (4) recurrent ischemic stroke in subjects with a prior ischemic stroke diagnosis. Prior events were assessed from the Patient Register and defined according to diagnosis of either myocardial infarction (International Classification of Diseases [ICD] 8 and ICD-9 code 410 and ICD-10 code I21) or ischemic stroke (ICD-8 codes 432-437, ICD-9 codes 4330-4379, and ICD-10 code I63). The total sample sizes for each outcome are shown in Fig 1.

Medication exposure

From the national Swedish Prescribed Drug Register, all claimed prescriptions of montelukast (Anatomical Therapeutic Chemical [ATC] code R03DC03) were identified in the study cohort between July 1, 2005, and December 31, 2008. In addition, data on other dispensed medications were collected and included in the analysis, as described below. Montelukast use was analyzed as a time-dependent variable, splitting the risk time according to nonuse (unexposed) and use (exposed). Calculated from the dispense date, subjects were considered exposed for 3 months based on the prescription length of 3 months of use.

Follow-up and outcome

Acute myocardial infarction (ICD-10 code I21) and ischemic stroke (ICD-10 code I63) were monitored as outcomes in separate analyses and defined according to either the primary diagnosis or the primary cause of death, as recorded in the Patient and Cause of Death Registers. The positive predictive values (ie, validity) of the myocardial infarction and ischemic stroke diagnoses in the Swedish Patient Register have been demonstrated to be around 95% when only primary diagnoses are considered.^{11,12}

Comorbidity and socioeconomic status

Information about asthma and chronic obstructive pulmonary disease (COPD) diagnoses was collected from the Patient Register as a proxy for respiratory tract disease, which is a likely confounder of studied associations between montelukast and cardiovascular disease. In addition, data for atrial fibrillation diagnosis were collected for the stroke analysis. Information on the use of different drugs for respiratory and cardiovascular diseases was used as a proxy for these respective diseases, which also could be considered potential

confounders. The use of cardiovascular drugs was indicative of pre-existing conditions with an increased risk of myocardial infarction and stroke, as shown in Tables E1 and E2 in this Online Repository at www.jacionline.org.

Data were collected from the Prescribed Drug Register on the use of inhaled corticosteroids, β -agonists, or both (ATC codes R03BA and R03A), inhaled anticholinergics (ATC code R03BB), oral steroids (ATC code H02), theophylline (ATC code R03DA), cromoglycate (ATC code R03BC), low-dose acetylsalicylic acid (B01AC06), dipyridamole (ATC code B01AC07), warfarin (ATC code B01AA03), angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor antagonists (ATC code C09), β -blockers (ATC code C07), calcium blockers (ATC code C08), and lipid-lowering drugs (ATC code C10). These variables (diagnosis and drug use) were modeled as time-dependent covariates, and subjects were considered nonaffected until the first occurrence of the respective covariate but thereafter affected.

Educational level and total yearly income were collected for the year 2005 and used as proxies for socioeconomic status. Educational level was categorized into 3 groups (high, college or university studies; middle, 2 or 3 years of high school; and low, 0-9 years of primary and secondary school), and yearly income (from employment, capital, real estate, and business activities) was categorized into tertiles.

Statistical analysis

The associations between montelukast use and the 4 outcomes (incident and recurrent myocardial infarction and ischemic stroke) were examined by calculating unadjusted incidence rates (ie, number of events per 1000 person-years at risk) with 95% CIs based on the Poisson distribution. Cox proportional hazard models were used to estimate the hazard ratios (HRs) of the drug use, with either partial adjustment for age, sex, and socioeconomic factors (education level and income) or with full adjustment, which also included the presence of respiratory disease and the use of drugs for respiratory and cardiovascular disease.

All sets of models were analyzed both for incident and recurrent events, as described above (all diagnosed separately). The statistical software package SAS 9.2 (SAS Institute, Inc, Cary, NC) was used for all analyses.

RESULTS

The baseline characteristics of the study population for myocardial infarction are shown in Table I, and those for stroke are shown in Table II. The numbers of montelukast users in each group are indicated in Tables I and II. The montelukast exposure was 0.6% in subjects without prior myocardial infarction and stroke and 0.5% in the study samples assessed for recurrent events. The number of events, event rates, and HRs for incident and recurrent myocardial infarction are shown in Table III, and those for incident and recurrent stroke are shown in Table IV.

The analyses indicated an association of montelukast use with an increased risk for a first-incident myocardial infarction when data were adjusted for age, sex, and socioeconomic status (Table III). However, in the fully adjusted analysis, taking into account potential confounders, as described in the Methods section and listed in Tables I and II, there was no association of montelukast use with incident myocardial infarction (Table III). In exploratory analyses we observed that the strongest confounders of the association of montelukast with myocardial infarction were the presence of COPD and the use of theophylline and oral steroids (attenuations from the partially adjusted model: HR, 1.48 [95% CI, 1.30-1.70] to 1.28 [95% CI, 1.13-1.45]; HR, 1.37 [95% CI, 1.21-1.55]; and HR, 1.19 [95% CI, 1.05-1.35] for COPD, theophylline, and oral steroids, respectively). In a model adjusting for age, sex, socioeconomic status, and all 3 covariates, the association was nonsignificant (HR, 1.05; 95% CI, 0.93-1.19). The results for each covariate in the myocardial infarction analysis are shown in Table E1.

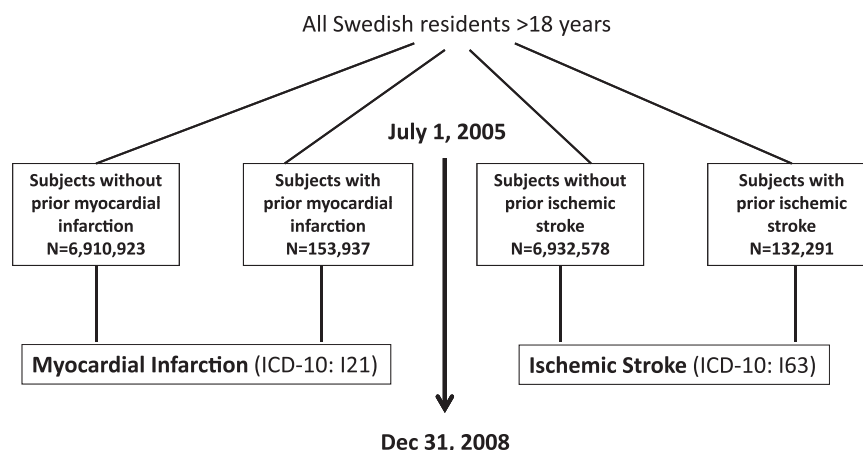


FIG 1. Schematic representation of the cohorts followed from July 1, 2005, to December 31, 2008, for the evaluation of incident and recurrent myocardial infarction and stroke.

TABLE I. Baseline characteristics of the myocardial infarction study samples

Outcome	Incident myocardial infarction		Recurrent myocardial infarction	
	Exposed	Unexposed	Exposed	Unexposed
No.	39,833	6,871,090	827	153,110
Mean age (y)	51.43	49.87	65.29	66.67
Female sex (%)	61.74	51.23	42.56	33.90
Educational level (%)				
Low	17.56	19.44	62.76	67.68
Mid	48.00	49.79	27.81	24.32
High	34.44	30.76	9.43	8.00
Income (%)				
Low	25.01	26.51	35.67	36.74
Mid	49.65	48.82	50.54	49.99
High	25.34	24.67	13.78	13.28
Asthma (%)	31.95	1.32	35.31	1.95
COPD (%)	7.91	0.82	31.08	4.40
Drug prescriptions (%)				
ICSs and/or β -agonists	89.46	10.30	90.57	14.38
Inhaled anticholinergics	13.10	0.96	33.74	4.23
Oral steroids	58.05	9.84	64.33	16.39
Theophylline	5.57	0.22	12.45	1.01
Cromoglycate	1.11	0.04	0.48	0.03
Low-dose ASA	12.59	11.39	76.18	83.51
β -Blockers	15.45	15.48	66.02	80.64
Calcium antagonists	13.01	8.35	35.07	27.80
ACE inhibitors and/or ARBs	20.74	13.81	64.45	60.65
Lipid-lowering drugs	16.37	11.15	74.37	70.22

ARB, Angiotensin receptor blocker; ASA, acetylsalicylic acid; ICS, inhaled corticosteroid.

TABLE II. Baseline characteristics of the stroke study samples

Outcome	Incident ischemic stroke		Recurrent ischemic stroke	
	Exposed	Unexposed	Exposed	Unexposed
No.	40,041	6,892,537	655	131,636
Mean age (y)	51.52	49.90	66.34	69.49
Female sex (%)	61.42	50.90	56.64	47.98
Educational level (%)				
Low	17.79	19.48	63.51	73.66
Mid	48.00	49.79	26.87	19.23
High	34.44	30.76	9.62	7.11
Income (%)				
Low	25.01	26.51	42.29	45.16
Mid	49.69	48.93	47.63	44.39
High	25.32	24.69	10.08	10.46
Asthma (%)	32.04	1.32	31.76	1.80
COPD (%)	8.10	0.85	28.70	3.48
Atrial fibrillation (%)	2.98	2.56	13.89	15.38
Drug prescriptions (%)				
ICSs and/or β -agonists	89.55	10.35	86.87	12.33
Inhaled anticholinergics	13.26	0.98	31.30	3.69
Oral steroids	58.16	9.90	60.31	14.41
Theophylline	5.55	0.21	16.64	1.45
Cromoglycate	1.10	0.04	0.76	0.02
Low-dose ASA	13.13	11.92	65.19	67.30
Dipyridamole	0.40	0.34	11.45	10.29
Oral anticoagulants	3.54	2.66	16.49	18.31
ACE inhibitors and/or ARBs	21.22	14.25	52.21	45.20
Lipid-lowering drugs	17.15	11.87	48.85	41.92

ARB, Angiotensin receptor blocker; ASA, acetylsalicylic acid; ICS, inhaled corticosteroid.

Two-way interactions between montelukast and sex were nonsignificant for incident stroke ($P = .66$), recurrent stroke ($P = .39$), and incident myocardial infarction ($P = .93$). For recurrent myocardial infarction, there was a significant interaction between montelukast use and sex ($P = .011$).

In subjects with a prior myocardial infarction, montelukast use was not significantly associated with the occurrence of a recurrent myocardial infarction in either the partially or fully adjusted analysis (Table III). A stratified analysis according to sex based on

significant interaction (see above) revealed no significant association of montelukast use with recurrent myocardial infarction in female subjects in the fully adjusted analysis, whereas montelukast use was associated with a significantly lower risk for recurrent myocardial infarction in male subjects (Table III).

There was a significantly reduced risk for stroke associated with montelukast use in patients with a prior stroke when adjusting for age, sex, and socioeconomic factors (Table IV). This protective effect remained unchanged, although with slightly

TABLE III. HRs for myocardial infarction according to montelukast use in subjects without and with prior myocardial infarction, respectively (nonuse was used as reference level)

	No. of events	Event rate (per 1000 PYAR)	Partially adjusted*		Fully adjusted†	
			HR (95% CI)	P value	HR (95% CI)	P value
Incident events	78,843	3.26 (3.24-3.28)	1.48 (1.3-1.7)	<.0001	0.97 (0.85-1.1)	.58
Recurrent events	18,620	40.7 (40.1-41.3)	1.21 (0.93-1.6)	.15	0.93 (0.71-1.2)	.58
Female subjects	6,844	46.3 (45.2-47.4)	1.69 (1.2-2.4)	<.01	1.25 (0.89-1.8)	.19
Male subjects	11,776	38.8 (38.2-39.6)	0.82 (0.5-1.2)	.34	0.65 (0.43-0.99)	.046

Because of a significant interaction with sex, adjusted HRs for recurrent myocardial infarction were stratified according to sex.

PYAR, Person-years at risk.

*Adjusted for age, sex, and socioeconomic status.

†Adjusted for all parameters listed in Table I.

TABLE IV. HRs for ischemic stroke according to montelukast use in subjects without and with prior ischemic stroke, respectively (nonuse was used as reference level)

	No. of events	Event rate (per 1000 PYAR)	Partially adjusted*		Fully adjusted†	
			HR (95% CI)	P value	HR (95% CI)	P value
Incident events	61,723	2.54 (2.52-2.56)	1.10 (0.93-1.3)	.29	0.95 (0.80-1.1)	.54
Recurrent events	13,596	36.6 (36.0-37.2)	0.62 (0.38-0.99)	.04	0.62 (0.39-1.0)	.05

PYAR, Person-years at risk.

*Adjusted for age, sex, and socioeconomic status.

†Adjusted for all parameters listed in Table II.

wider CIs, in the fully adjusted analysis, taking into account all factors listed in Table II.

For incident ischemic stroke, 2-way interaction tests did not reveal any significant interactions for montelukast exposure and any of the covariates listed in Table II. In contrast, there was a significant interaction for montelukast use and the use of ACE inhibitors/angiotensin receptor blockers (ATC code C09) in the analysis for recurrent stroke ($P = .029$). Stratification according to exposure to this class of drugs revealed that although montelukast exposure was not associated with recurrent stroke in ACE inhibitor/angiotensin receptor blocker users (HR, 0.97; 95% CI, 0.55-1.72), montelukast was significantly associated with a reduced risk for recurrent stroke in patients not taking ACE inhibitors/angiotensin receptor blockers (HR, 0.34; 95% CI, 0.14-0.82). The HRs associated with each covariate in the fully adjusted model with ischemic stroke as outcome are shown in Table E2.

Further adjustment for rural/urban residence did not significantly alter the results for any of the analyses (data not shown).

DISCUSSION

The results of the present nationwide population-based study provide a first indication that LTRAs, in addition to their effects in asthmatic patients, might also affect the clinical outcomes of atherosclerotic vessel disease. Although the present study is limited to registry data, the results provide a first suggestion that montelukast use might be associated with a lower risk of recurrent events. The mechanism behind a secondary preventive effect of montelukast could potentially be explained by the antagonism of leukotriene-induced proinflammatory signaling.

Asthma is the only current indication for montelukast, either as add-on treatment if symptoms are not controlled by inhaled corticosteroid and β -agonists or for symptomatic relief of allergic rhinitis in asthmatic patients. Because asthmatic patients can exhibit an increased risk for incident coronary disease and

cerebrovascular disease¹³⁻¹⁵ asthma must be considered as a confounder for the association of montelukast with the increased risk of incident myocardial infarction in the present study after adjustment for age, sex, and socioeconomic factors. Our exploratory analyses of confounders for the montelukast-myocardial infarction association indicated that the use of theophylline and oral steroids, as well as a diagnosis of COPD, were the major confounders for this association of montelukast with incident myocardial infarction. In the fully adjusted analysis, taking into account also respiratory diagnoses and treatments, no effects were observed for montelukast on incident myocardial infarction or stroke in the present study. In summary, these observations suggest no major effects of montelukast on incident atherosclerotic vessel disease on a population basis.

In contrast to this lack of primary prevention, the present study provides a first suggestion for protective effects of montelukast in secondary prevention. Whereas no significant associations with recurrent myocardial infarction were observed in the present study, a stratified analysis according to sex based on significant interactions suggested that montelukast use was associated with a lower risk of recurrent myocardial infarction in male but not in female subjects. In addition, montelukast use was associated with a lower risk of recurrent stroke. Adjusting the latter finding also for potential confounders, such as diagnosis of asthma, COPD, or atrial fibrillation, as well as for the use of respiratory and cardiovascular drugs, revealed similar point estimates and suggested a borderline significant protective effect of montelukast in the secondary prevention of ischemic stroke.

There are several possible reasons for the differential effects of montelukast in primary and secondary prevention. The event rate was almost 15-fold lower in the general population compared with that seen in subjects with a prior event. Furthermore, longer treatment periods might be needed to detect effects in primary prevention, and the 3.5 years of exposure data available in the present study might have been insufficient to detect primary preventive effects. Nevertheless, these findings are in line with the

lack of protective effects observed for aspirin in prospective studies evaluating primary prevention of stroke and with the fact that current guidelines do not recommend pharmacologic interventions to prevent incident stroke in the general population.¹⁶ In contrast, recommendations for secondary prevention include antiplatelet therapy, oral anticoagulants (if embolic stroke), lipid-lowering therapy, and treatment of hypertension,¹⁷ all of which were taken into account in the present study, suggesting an additive protective effect of montelukast in secondary stroke prevention. Nevertheless, our exploratory analysis based on significant interactions indicated that the association of montelukast with a decreased risk for recurrent stroke was observed only in patients not taking ACE inhibitors or angiotensin receptor blockers, suggesting that leukotrienes and angiotensin II might activate similar signaling pathways in the context of stroke protection. A link between angiotensin II and leukotriene signaling has also received support from experimental studies.¹⁸ However, the exact relation between antileukotrienes and angiotensin-modifying drugs remains to be established.

The large sample size represents one of the strengths of the present study and allows the study of the association between montelukast and cardiovascular events in the general population for primary prevention, as well as in a large number of subjects with prior cardiovascular disease for secondary prevention, with adjustment of the most relevant confounders. Nevertheless, the lack of information on some cardiovascular risk factors, such as smoking, obesity, blood pressure, and lipid levels, must be acknowledged as an important limitation. Adjustment for lipid-lowering drugs and other cardiovascular medications was used as proxy for dyslipidemia and hypertension to compensate for this limitation. Likewise, based on previous studies that have established a correlation between smoking and socioeconomic status,¹⁹ the adjustment for educational level and income in the present study served also as a proxy for smoking. It should also be pointed out that the adherence to treatment is unknown but that the use of dispensed medications and not prescriptions to define exposure in the present study is likely to identify compliers with treatment and not only to reflect the intention to treat. Finally, reversed causation cannot be excluded because patients with better prognosis might have been more likely to receive adequate asthma treatment, and it should be acknowledged that the nonrandomized observational design of the present study means that no causality can be definitively attributed and that associations could be driven by unknown confounding.

There are several potential mechanisms behind the observed effect of montelukast on recurrent stroke. Experimental studies have established that leukotriene signaling through the CysLT₁ receptor (which is the target for montelukast) induces leukocyte activation and recruitment, vascular smooth muscle migration and proliferation, and endothelial activation, all of which potentially could be involved in the progression of atherosclerotic vessel disease.⁵ Furthermore, *in vivo* murine models have shown that montelukast treatment retards atherosclerotic lesion growth.²⁰ Human carotid atherosclerotic lesions express the CysLT₁ receptor, as well as 5-lipoxygenase and other CysLT-synthesizing enzymes.²¹ Furthermore, 5-lipoxygenase promoter polymorphisms, originally described in asthmatic patients,²² have been associated with subclinical atherosclerosis measured as an increased intima-media thickness of the carotid artery,²³ and CysLT production is increased in patients with an atherosclerotic plaque detected on carotid ultrasonography.²⁴ In a study of patients

undergoing vascular surgery for carotid artery stenosis, 5-lipoxygenase expression and leukotriene production correlated with either clinical or radiologic signs of cerebral ischemia, suggesting that leukotriene signaling might be involved in atherosclerotic plaque rupture.²⁵ In support of the latter suggestion, a genetic association study identified that haplotypes in the promoter of *ALOX5AP*, which encodes another protein involved in leukotriene synthesis, predicted a nearly 2-fold greater risk of stroke.⁸ Finally, in addition to potential effects related to atherosclerosis development, progression, and plaque rupture, antagonism of the CysLT₁ receptor has also been shown to limit stroke severity in experimental cerebral ischemia and reperfusion.⁷

In conclusion, the present findings suggesting a potential risk reduction for recurrent cardiovascular events as a result of montelukast use are novel, and it is therefore important that additional studies are performed to confirm our results and assess their therapeutic implications. In particular randomized controlled trials of montelukast in patients with a first stroke are needed to evaluate antileukotriene treatment for secondary stroke prevention.

Clinical implications: Although antileukotrienes are solely used in the treatment of asthma, our study provides a first indication for a potential protective role of the antiasthma drug montelukast for cardiovascular disease.

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TABLE E1. HRs (95% CIs) for each covariate in the fully adjusted model with myocardial infarction as outcome

Outcome	Incident myocardial infarction	Recurrent myocardial infarction
Age	1.07 (1.071-1.072)	1.02 (1.021-1.024)
Male sex	2.51 (2.47-2.56)	1.54 (1.49-1.59)
Educational level		
Low	1.25 (1.21-1.29)	1.32 (1.23-1.43)
Mid	1.35 (1.31-1.39)	1.16 (1.08-1.26)
Income		
Low	2.22 (2.16-2.27)	2.48 (2.34-2.63)
Mid	1.17 (1.15-1.20)	1.06 (1.00-1.12)
Asthma	0.99 (0.94-1.05)	0.99 (0.90-1.09)
COPD	1.46 (1.40-1.53)	1.31 (1.22-1.41)
Drug prescriptions		
ICSs and/or β -agonists	1.14 (1.11-1.17)	0.99 (0.93-1.03)
Inhaled anticholinergics	1.19 (1.14-1.25)	1.22 (1.12-1.32)
Oral steroids	1.43 (1.40-1.46)	1.37 (1.31-1.43)
Theophylline	1.27 (1.17-1.37)	1.25 (1.08-1.44)
Cromoglycate	0.92 (0.61-1.40)	2.28 (1.23-4.24)
Low-dose ASA	1.33 (1.31-1.35)	0.98 (0.94-1.01)
β -Blockers	1.36 (1.34-1.38)	1.11 (1.07-1.15)
Calcium antagonists	1.24 (1.22-1.26)	1.27 (1.22-1.31)
ACE inhibitors and/or ARBs	1.33 (1.31-1.36)	1.28 (1.25-1.33)
Lipid-lowering drugs	1.14 (1.11-1.16)	0.66 (0.64-0.68)

ARB, Angiotensin receptor blocker; ASA, acetylsalicylic acid; ICS, inhaled corticosteroid.

TABLE E2. HRs (95% CIs) for each covariate in the fully adjusted model with ischemic stroke as outcome

Outcome	Incident ischemic stroke	Recurrent ischemic stroke
Age	1.08 (1.076-1.078)	1.02 (1.016-1.020)
Male sex	1.48 (1.46-1.51)	1.26 (1.21-1.31)
Educational level		
Low	1.30 (1.25-1.34)	0.89 (0.82-0.96)
Mid	1.27 (1.22-1.31)	1.01 (0.94-1.09)
Income		
Low	1.55 (1.50-1.59)	1.23 (1.15-1.30)
Mid	1.20 (1.16-1.23)	0.93 (0.88-0.98)
Asthma	1.05 (0.98-1.12)	1.00 (0.87-1.15)
COPD	1.07 (1.01-1.13)	1.11 (1.00-1.24)
Atrial fibrillation	1.79 (1.74-1.84)	1.36 (1.29-1.42)
Drug prescriptions		
ICSs and/or β -agonists	1.01 (0.98-1.04)	0.99 (0.92-1.06)
Inhaled anticholinergics	1.05 (0.99-1.11)	0.87 (0.76-0.99)
Oral steroids	1.18 (1.15-1.21)	1.05 (0.99-1.12)
Theophylline	0.77 (0.68-0.88)	0.79 (0.63-1.01)
Cromoglycate	0.95 (0.58-1.56)	1.19 (0.30-4.75)
Low-dose ASA	1.59 (1.56-1.63)	1.12 (1.08-1.17)
Dipyridamole	2.12 (1.99-2.26)	1.38 (1.31-1.46)
Oral anticoagulants	0.97 (0.93-1.00)	0.91 (0.86-0.97)
ACE inhibitors and/or ARBs	1.38 (1.35-1.40)	1.08 (1.04-1.12)
Lipid-lowering drugs	1.02 (1.00-1.04)	0.99 (0.95-1.03)

ARB, Angiotensin receptor blocker; ASA, acetylsalicylic acid; ICS, inhaled corticosteroid.