Montelukast Use Decreases Cardiovascular Events in Asthmatics

Malvina Hoxha[1], Calogero Tedesco[2], Silvana Quaglini[3], Visar Malaj[4], Linda Pustina[5], Valerie Capra[6], Jilly Evans[7], Angelo Sala[6], and G Enrico Rovati[6]

[1]Catholic University Our Lady of Good Counsel
[2]Centro Cardiologico Monzino IRCCS
[3]University of Pavia
[4]University of Tirana
[5]Ministry of Education and Sports
[6]University of Milan
[7]University of Pennsylvania

July 1, 2020

Abstract

Background: Cysteinyl leukotrienes are pro-inflammatory mediators with a clinically established role in asthma and a potential human genetic and preclinical role in cardiovascular diseases. Given that cardiovascular disease has a critical inflammatory component, the use of a leukotriene antagonist may represent an innovative therapy to target inflammation in cardiovascular prevention. Methods: We performed an observational retrospective (three years) study on eight hundred asthmatic patients 18 years or older in Albania, equally classified in two cohorts, exposed or non-exposed to montelukast, matched by age and gender. Patients with a previous history of myocardial infarction or ischemic stroke were excluded. Results: we considered eight hundred asthmatic patients (368 male and 432 female) 18 years or older. Overall 37 (4.6%) of the asthmatic patients, 32 non-exposed and 5 exposed, suffered a major cardiovascular event during the 3 years observation period. All the cardiovascular events occurred among patients with an increased cardiovascular risk. Thus, we used both a propensity score (PS) matching and a PS adjusted Cox model for analysis. In both analyses exposure to montelukast remained a significant protective factor for incident ischemic events (HR = 0.222; HR = 0.241, respectively), independently from gender. The event-free Kaplan-Meier survival curves confirmed the lower cardiovascular incidence of patients exposed to montelukast (p = <0.0001). Conclusion: Collectively, our data indicates that there is a potential protective role of montelukast for incident ischemic events in the older asthmatic population, suggesting a co-morbidity benefit of montelukast in asthmatics and possible innovative therapy to target inflammation for cardiovascular prevention.

Introduction

Inflammation is a physiological reaction that can become a pathological effect, associated with several diseases and characterized by the release of mediators, including metabolites of the arachidonic acid cascade. Cysteinyl leukotrienes (cysteinyl-LTs), namely LTC_4, LTD_4, and LTE_4, are potent pro-inflammatory lipid mediators long known to play an important role in asthma[1], that have also been implicated in other inflammatory conditions, such as allergic rhinitis (AR), atopic dermatitis, and urticarial[2]. Additionally, their involvement has been hypothesized in several cardiovascular diseases (CVDs), such as acute myocardial infarction (MI), ischemic stroke (IS), atherosclerosis, aortic aneurysms and intimal hyperplasia[3-6]. Increased intracoronary production of cysteinyl-LTs was detected in patients undergoing coronary angioplasty[7] and by systemic urinary LTE_4 excretion in acute MI and ischemic heart disease patients[8-10]. Several proteins in the 5-lipoxygenase pathway, including both CysLT receptors, were found in the arterial wall of patients at

different stages of atherosclerosis[11-14]. Finally, besides the increase in cysteinyl-LTs concentration in CVDs, a number of genetic studies also support a link between cysteinyl-LTs, their receptors and CVD[15-18].

In the 1990s, after the discovery that cysteinyl-LTs were implicated in asthma, a number of LT modifiers, i.e. 5-lipoxygenase pathway inhibitors, but particularly $CysLT_1$ receptor antagonists (LTRAs), were developed and are now widely used to treat asthma and other allergic conditions[19]. However, CVDs, particularly atherosclerosis, have a crucial inflammatory component[20,21], and given the role of cysteinyl-LTs in modulating vascular tone and inflammation[22-24], LTRAs have been proposed as potential therapeutics for such diseases[6,25]. The potent and selective $CysLT_1$ receptor antagonist montelukast was first approved by the Food and Drug Administration to be used in different stages of asthma both in adults and children and later on also for the treatment of seasonal and perennial AR[19]. In addition, in preclinical animal models, montelukast has been shown to significantly reduce the formation of atherosclerotic plaques and intimal hyperplasia, and to reduce the level of reactive oxygen species production and apoptosis, demonstrating beneficial effects on endothelial cells functions and myocardial remodeling (see[26] and[6] for recent reviews). Furthermore, montelukast has been demonstrated to inhibit oxidized low-density lipoprotein-induced monocyte adhesion to endothelial cells, suggesting a protective role in the early stages of atherosclerosis[27]. Montelukast also protects against aorta dilatation and reduces aortic rupture and aneurism development in three independent animal models of abdominal aortic aneurysm[28].

Therefore, considerable data exists in CVD for a role of LTRAs in general, and of montelukast in particular, in controlling and reducing CV risk[25,29]. Indeed, asthmatic patients receiving montelukast have lower levels of CV disease-associated inflammatory biomarkers and lipid levels[30], while a recent nationwide cohort study on incident or recurrent ischemic events provided a first indication for a role of montelukast for secondary prevention of CVDs[31]. In order to explore a potential complementary approach to other agents for CVD prevention, we performed an observational retrospective study including eight hundred asthmatic patients exposed or non-exposed to montelukast to assess the efficacy of montelukast in prevention of a major CV event such as MI o

Methods

Data collection

To obtain a significant sample of Albanian asthmatic population, a number of allergists/pathologists around the country were enrolled to contribute to the study by providing data about asthmatic subjects (18 years or older) based on their patient register and medical history. The study was retrospective, and medical records of 400 asthmatic subjects receiving montelukast (10 mg daily) and 400 asthmatic subjects not receiving montelukast were evaluated (from January 1st, 2012 to December 31st, 2014). Asthmatic subjects (International Classification of Diseases (ICD-10 v:2016) code 493) were diagnosed on the basis of GINA (Global Initiative for Asthma) criteria (https://ginasthma.org) on objective evidence of variable airflow obstruction. As the number of patients taking montelukast was the limiting factor of the study, we considered exposed all patients taking the drug for a period of at least three months, excluding all subjects with a previous history of MI or IS, as reported in their medical records (ICD: MI-I21 or IS-I63). These patients were randomly matched with patients not receiving montelukast as an anti-asthmatic drug primarily by gender and secondly by age. In order to identify a predisposition of the monitored patients to an increased CV risk for MI and IS, information was obtained on drug therapies for major chronic conditions such as hypertension, diabetes mellitus, dyslipidemia, cerebrovascular disease, anemia, arrhythmias, epilepsy, allergies, psychosis, ulcers, cancer, and depression. General information such as age, gender, patient education level, residence and income were also recorded, while systemic blood pressure, body mass index, smoking, obesity or cholesterol were not available for the majority of the patients and for this reason were not taken into account in our analysis. According to ICD, the two groups were finally classified for the presence or absence of MI or IS.

Study power

We calculated that, for a two groups survival analysis comparison on a total time of 3 years and 400 patients per group, we able to detect as significant an HR of 0.8 or lower with a type 1 error alpha = 0.05 and a

power of 80%.

Statistical analysis

Median and interquartile range (Q1 – Q3) was used to describe age distribution due to its non-normality. As well, the non-parametric Wilcoxon test was used to assess the difference of age between the two groups of patients exposed or non-exposed to montelukast. Pearson's Chi-square test for association was used to test the association of montelukast exposure with the qualitative variables. All the available variables were, potentially, considered as predictors of a CV event. However, because some drugs were used by less than 10 patients, those were not considered in the subsequent analysis. Cox (proportional hazards) regression analysis was performed pooling IS and MI as target events. All the CV events occurred among patients taking anti-hypertensive, anti-platelet, or anti-cholesterol drugs, i.e. among patients at increased 'CV risk'. For this reason, those variables could not be included in a classical Cox regression models, but rather we used both a propensity score (PS) matching using different calipers (0.4-01) and a Cox model adjusted for PS. Since our study is a retrospective one, PS method was used for reducing the effects of confounders. PS has been calculated using a logistic regression on the treatment variable (i.e. exposure to montelukast), considering age, gender, residence, education, income, as well as anti-hypertensive, anti-platelet, diuretic, hypoglycemic, anti-hypercholesterolemic and anti-androgen drugs as potential predictors of taking treatment. Concerning qualitative ordinal variables with more than two levels, analyses were performed both using all levels and aggregating levels in order to obtain binary variables. IS or MI were considered as events for survival analysis. For every patient the observation started January 1st, 2012. All the patients have been observed up to three years (no drop out) or until the first event. Event-free Kaplan-Meier survival curves were drawn for major CV events, and the difference between two curves was tested using the log-rank statistics. For all the analyses, p-values lower than 0.05 were considered statistically significant. All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, USA)

Results

Baseline characteristics and variable distribution in the patient sample, overall and according to montelukast use, are reported in Table 1.

We first analysed possible relationships between demographic features and montelukast usage. A significant difference was observed in the age of patients exposed (median = 60, 46 Q1 - 68 Q3) and non-exposed to montelukast (median = 64, 55.75 Q1 - 70 Q3). In addition, 77.7% of rural zones asthmatic (108/139) were exposed to montelukast, compared to only 44.2% of urban patients (292/661), while within low-education patients only 28.1% were exposed to montelukast (68/242), compared to 59.5% within mid+high education (332/558). Income did not show a significant relationship to montelukast use. The use of additional drugs appeared to be very balanced between the two cohorts, exposed and non-exposed to montelukast, with the exception of antiplatelet (5% vs. 9.75%) and antitumoral drugs. Overall, 37 (4.6%) of our asthmatic patients suffered a major CV event during the observation period. Interestingly, the overall incidence of an ischemic event in our asthmatic population (15.4 events per 1000 patient-years) is similar to the expected rate in a general population (between 8 and 18.1, depending on level of blood pressure[32]). However, considering only patients not exposed to montelukast, the incidence is higher (26.7 events per 1000 patient-years) than that observed in the non-asthmatic population, while the incidence in patients exposed to the drug is 4.17 events per 1000 patient-years, which is lower than expected in the general population[32]. The analysis of the incidence of CV events showed that the age of patients that did not experience a CV event (median = 62) was significantly (Wilcoxon test, $p < 0.00004$) lower when compared to patients suffering a CV event (median = 74), with 12 years difference between the two groups (Figure 1).

Results from Cox model using a PS matching, are shown in Tables 2. We performed PS matching with different calipers but we focused on a caliper = 0.2 because it has been demonstrated to be optimal in many settings[33] to look for predictors of a major CV event. PS matching lead to 269 patients in each group with a number of events of 22 resulting in a significant ($p = 0.0065$) protection in CV events (HR = 0.222) due

to montelukast use.

Because in the PS matching analysis we lost some of the events (15 out of 37, Table 2) we also used a Cox regression model adjusted for PS, which allowed us to take all the events into consideration (Table 3). Even though patients exposed to montelukast were overall younger than the ones not exposed to the drug, montelukast remained a significant (p = 0.0046 protective factor (HR = 0.241) for CV events. In addition, as the use of antiplatelet drugs was significantly different between exposed and not exposed to montelukast (Table 1), we also performed a Cox model adjusted for PS only on patients taking antiplatelet drugs. As shown in Table 3, the results are still statistically significant and not substantially different from those considering the whole sample.

In Figure 2 are reported the event-free Kaplan-Meier survival curves of patients exposed or not exposed to montelukast. On the left panel, the whole patient sample was considered, while on the right panel were considered only patients using antiplatelet drugs. In both cases the two curves resulted statistically different, while, as expected, the difference in survival probability was higher when limiting the analysis to patients treated with antiplatelets (Logrank test, p = <0.0001 vs. p = <0.0001).

Discussion

Our observational retrospective study of a homogenous population of eight hundred asthmatic adults in Albania has demonstrated a significant relationship between the use of montelukast and the reduction of an ischemic CV event such as IS or MI even after correction for possible confounders. Thus, our data indicate that, despite the limits of the present study, LTRAs in general and montelukast in particular may have a positive impact in the prevention of CV disease in asthmatic patients.

Ischemic events such as MI and IS are among the leading causes of death worldwide. Atherosclerosis has been recognized to have a crucial inflammatory component[20,21], and there is an unmet need for an anti-inflammatory treatment capable of reducing CVD risk[34]. Since atherosclerotic coronary arteries respond to cysteinyl-LTs[11,12] and the variation of the gene encoding the 5-lipoxygenase activating protein (FLAP), an essential protein for cysteinyl-LT biosynthesis, is associated to an increased risk of MI[15,35], we hypothesized that LTRAs may have a role in CVD prevention[29]. Asthmatic patients are more predisposed to CV events than the non-asthmatic population[36,37] and inflammation is a common feature of both asthma and atherosclerosis, so the use of a LTRA in asthmatic patients may have additional, complementary therapeutic benefit.

Analysis of montelukast usage in our sample population of asthmatic patients in Albania showed that patients treated with the drug were on average four years younger than those in the non-exposed montelukast group, however, with a median age less than 65 years for both groups. The clinical relevance of this modest difference between groups is uncertain, and considering the huge difference in the reported incidence of CVDs between male and female (http://www.who.int/healthinfo/global_burden_disease/GBD_report_2004update_full.pdf) we used gender as primarily matching criteria and age as secondary criteria for inclusion.

As expected, the average age of patients incurring CV events, irrespective of montelukast treatment, was older than those without CV events. This age-related increase in ischemic events indicates a substantial contribution of age to the CV risk, as one might expect in the aging population[38].

Both PS matching and PS adjusted Cox analysis reveals that, despite age difference, exposure to montelukast remains a significant protective factor for incident ischemic events, independently from gender. This observation extends to primary prevention the results of Ingelsson and co-authors, who observed an effect of montelukast on recurrent MI in male and of recurrent IS in both genders, but no association of montelukast use with incident events[31]. Because asthma is recognized to be a possible confounder for the association of montelukast with CV diseases, limiting the sample to asthmatic subjects, as in our study, could have facilitated the detection of the effect of montelukast on incident events. All the events observed in our study occurred among patients taking anti-hypertensive, diuretic, anti-platelet or anti-cholesterol drugs, namely patients at increased CV risk of ischemic events.

Notably, analysis of the data relative to the concomitant use of these drugs, possible confounders for the association of montelukast to CV risk, excluded their potential influence on the CV event rate. In fact, while all the other drugs were balanced in the two groups, only the use of antiplatelet drugs was statistically different. Therefore, to further corroborate our findings and to exclude that use of antiplatelet drugs might bias our results, we also performed a PS adjusted Cox analysis only on patients taking antiplatelet drugs. This, again resulted in a statistically significant protective effect of montelukast not substantially different from that obtained in the overall sample.

Event-free Kaplan-Meier survival curves for patients treated and non-treated with montelukast are statistically different, with a clear statistical significance observed also if calculated only in patients taking antiplatelet drugs. Collectively, these observations suggest that anti-inflammatory drugs such as LTRAs may have a significant protective effect in the prevention of ischemic events in asthmatics. Finally, our study could even have underestimated the protective effect of montelukast, since we considered as exposed also patients that had the event after stopping the drug. Indeed, only 2 out of 5 events in the exposed group occurred during the treatment, strengthening our perception of possible protection associated to montelukast use.

We acknowledge that there are a number of limitations of this study, such as the relatively limited number of events observed. Yet, our cohort is perfectly balanced for gender, a significant factor for CV diseases, and homogeneous with respect to asthma indication, which is recognized to be a confounding factor in the Ingelsson study[31]. Therefore, despite the number of events in the two studies are largely different, our subject sample might provide increased sensitivity describe in detecting the protective effect of montelukast, particularly in a population known to have an higher incidence of CV diseases. In addition, other possible risk factors such as systemic blood pressure, body mass index, smoking, obesity, alcohol or physical inactivity, were not available for the majority of the patients, similarly to the Ingelsson study[31], and could not be included in our investigation. Conversely, the concomitant use of other drugs is well balanced between the two cohorts, with exception of the use of antiplatelet drugs which, nevertheless, does not seem to have an influence on the CV event rate. Therefore, we are confident that the significance of montelukast protection evidenced has not been biased by these possible confounders.

We believe that our data should foster a larger, case-control trial taking into consideration all the CV risk factors that are missing in this study and that was only possible to account for using treatments as proxies. Montelukast patent is, however, expired, limiting the interest of the pharmaceutical industry to fund such an expensive CV trial. Thus, despite the impact that a definitive confirmation of these data might have on public health, only non-profit organization or government supported grants might provide enough funding for such a large study.

In conclusion, our observational study highlights an additional benefit of leukotriene modifiers in CVDs, suggesting montelukast as a controller in asthmatic patients with coronary artery disease risk factors. Targeting the cysteinyl-LT pathway, or indeed the total LT pathway with FLAP inhibitors, may be a strategy for primary prevention in populations at increased CV risk, or secondary prevention in the general population. LTRAs in general and montelukast in particular are approved drugs used in the clinical practice since almost two decades, and have been demonstrated, over the years, to be well tolerated[39]. The use of LT antagonists or inhibitors as anti-inflammatory agents in the CV setting may have a beneficial effect in reducing ischemic events that are among the leading causes of death in the developed world.

References

1. Nicosia S, Capra V, Rovati GE. Leukotrienes as mediators of asthma.*Pulmonary Pharmacology & Therapeutics.* 2001;14(1):3-19.

2. Capra V, Thompson MD, Sala A, Cole DE, Folco G, Rovati GE. Cysteinyl-leukotrienes and their receptors in asthma and other inflammatory diseases: Critical update and emerging trends. *Med Res Rev.* 2007;27(4):469-527.

3. Folco G, Rossoni G, Buccellati C, Berti F, Maclouf J, Sala A. Leukotrienes in cardiovascular diseases. *Am J Respir Crit Care Med.* 2000;161(2 Pt 2):S112-116.

4. Back M. Leukotriene signaling in atherosclerosis and ischemia. *Cardiovasc Drugs Ther.* 2009;23(1):41-48.

5. Poeckel D, Funk CD. The 5-Lipoxygenase/Leukotriene Pathway in Preclinical Models of Cardiovascular Disease. *Cardiovasc Res.*2010.

6. Capra V, Back M, Barbieri SS, Camera M, Tremoli E, Rovati GE. Eicosanoids and their drugs in cardiovascular diseases: focus on atherosclerosis and stroke. *Med Res Rev.* 2013;33(2):364-438.

7. Brezinski DA, Nesto RW, Serhan CN. Angioplasty triggers intracoronary leukotrienes and lipoxin A4. Impact of aspirin therapy. *Circulation.* 1992;86(1):56-63.

8. Carry M, Korley V, Willerson JT, Weigelt L, Ford-Hutchinson AW, Tagari P. Increased urinary leukotriene excretion in patients with cardiac ischemia. In vivo evidence for 5-lipoxygenase activation. *Circulation.* 1992;85(1):230-236.

9. Allen SP, Sampson AP, Piper PJ, Chester AH, Ohri SK, Yacoub MH. Enhanced excretion of urinary leukotriene E4 in coronary artery disease and after coronary artery bypass surgery. *Coron Artery Dis.*1993;4(10):899-904.

10. De Caterina R, Giannessi D, Lazzerini G, et al. Sulfido-peptide leukotrienes in coronary heart disease - relationship with disease instability and myocardial ischaemia. *Eur J Clin Invest.*2010;40(3):258-272.

11. Allen S, Dashwood M, Morrison K, Yacoub M. Differential leukotriene constrictor responses in human atherosclerotic coronary arteries. *Circulation.* 1998;97(24):2406-2413.

12. Lotzer K, Spanbroek R, Hildner M, et al. Differential leukotriene receptor expression and calcium responses in endothelial cells and macrophages indicate 5-lipoxygenase-dependent circuits of inflammation and atherogenesis. *Arterioscler Thromb Vasc Biol.*2003;23(8):e32-36.

13. Spanbroek R, Grabner R, Lotzer K, et al. Expanding expression of the 5-lipoxygenase pathway within the arterial wall during human atherogenesis. *Proc Natl Acad Sci U S A.* 2003;100(3):1238-1243.

14. Di Gennaro A, Wagsater D, Mayranpaa MI, et al. Increased expression of leukotriene C4 synthase and predominant formation of cysteinyl-leukotrienes in human abdominal aortic aneurysm. *Proc Natl Acad Sci U S A.* 2010;107(49):21093-21097.

15. Helgadottir A, Manolescu A, Thorleifsson G, et al. The gene encoding 5-lipoxygenase activating protein confers risk of myocardial infarction and stroke. *Nat Genet.* 2004;36(3):233-239.

16. Iovannisci DM, Lammer EJ, Steiner L, et al. Association between a leukotriene C4 synthase gene promoter polymorphism and coronary artery calcium in young women: the Muscatine Study. *Arterioscler Thromb Vasc Biol.* 2007;27(2):394-399.

17. Bevan S, Lorenz MW, Sitzer M, Markus HS. Genetic variation in the leukotriene pathway and carotid intima-media thickness: a 2-stage replication study. *Stroke.* 2009;40(3):696-701.

18. Freiberg JJ, Tybjaerg-Hansen A, Nordestgaard BG. Novel mutations in leukotriene C(4) synthase and risk of cardiovascular disease based on genotypes from 50,000 individuals. *J Thromb Haemost.*2010;8(8):1694-1701.

19. Capra V, Ambrosio M, Riccioni G, Rovati GE. Cysteinyl-leukotriene receptor antagonists: present situation and future opportunities. *Curr Med Chem.* 2006;13(26):3213-3226.

20. Ross R. Atherosclerosis–an inflammatory disease. *N Engl J Med.* 1999;340(2):115-126.

21. Back M, Hansson GK. Anti-inflammatory therapies for atherosclerosis. *Nat Rev Cardiol.* 2015;12(4):199-211.

22. Sala A, Rossoni G, Berti F, et al. Monoclonal anti-CD18 antibody prevents transcellular biosynthesis of cysteinyl leukotrienes in vitro and in vivo and protects against leukotriene-dependent increase in coronary vascular resistance and myocardial stiffness.*Circulation.* 2000;101(12):1436-1440.

23. Bäck M. Leukotriene receptors: crucial components in vascular inflammation. *ScientificWorldJournal.* 2007;7:1422-1439.

24. Back M, Powell WS, Dahlen SE, et al. International Union of Basic and Clinical Pharmacology. Update on Leukotriene, Lipoxin and Oxoeicosanoid Receptors: IUPHAR Review 7. *Br J Pharmacol.*2014;171(15):3551-3574.

25. Funk CD. Leukotriene modifiers as potential therapeutics for cardiovascular disease. *Nat Rev Drug Discov.* 2005;4(8):664-672.

26. Back M, Dahlen SE, Drazen JM, et al. International Union of Basic and Clinical Pharmacology. LXXXIV: leukotriene receptor nomenclature, distribution, and pathophysiological functions. *Pharmacol Rev.*2011;63(3):539-584.

27. Di X, Tang X, Di X. Montelukast inhibits oxidized low-density lipoproteins (ox-LDL) induced vascular endothelial attachment: An implication for the treatment of atherosclerosis. *Biochem Biophys Res Commun.* 2017;486(1):58-62.

28. Di Gennaro A, Araujo AC, Busch A, et al. Cysteinyl leukotriene receptor 1 antagonism prevents experimental abdominal aortic aneurysm.*Proc Natl Acad Sci U S A.* 2018;115(8):1907-1912.

29. Hoxha M, Rovati GE, Cavanillas AB. The leukotriene receptor antagonist montelukast and its possible role in the cardiovascular field. *Eur J Clin Pharmacol.* 2017;73:799-809.

30. Allayee H, Hartiala J, Lee W, et al. The effect of montelukast and low-dose theophylline on cardiovascular disease risk factors in asthmatics. *Chest.* 2007;132(3):868-874.

31. Ingelsson E, Yin L, Back M. Nationwide cohort study of the leukotriene receptor antagonist montelukast and incident or recurrent cardiovascular disease. *J Allergy Clin Immunol.*2012;129(3):702-707.

32. Tajeu GS, Booth JN, 3rd, Colantonio LD, et al. Incident Cardiovascular Disease Among Adults With Blood Pressure <140/90 mm Hg. *Circulation.* 2017;136(9):798-812.

33. Austin PC. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. *Pharm Stat.* 2011;10(2):150-161.

34. Rovati GE, Sala A, Capra V, Dahlen SE, Folco G. Dual COXIB/TP antagonists: a possible new twist in NSAID pharmacology and cardiovascular risk. *Trends Pharmacol Sci.* 2010;31(3):102-107.

35. Hakonarson H, Thorvaldsson S, Helgadottir A, et al. Effects of a 5-lipoxygenase-activating protein inhibitor on biomarkers associated with risk of myocardial infarction: a randomized trial. *Jama.*2005;293(18):2245-2256.

36. Iribarren C, Tolstykh IV, Miller MK, Sobel E, Eisner MD. Adult asthma and risk of coronary heart disease, cerebrovascular disease, and heart failure: a prospective study of 2 matched cohorts. *Am J Epidemiol.* 2012;176(11):1014-1024.

37. Tattersall MC, Guo M, Korcarz CE, et al. Asthma predicts cardiovascular disease events: the multi-ethnic study of atherosclerosis. *Arterioscler Thromb Vasc Biol.*2015;35(6):1520-1525.

38. Dhingra R, Vasan RS. Age as a risk factor. *Med Clin North Am.*2012;96(1):87-91.

39. Bisgaard H, Skoner D, Boza ML, et al. Safety and tolerability of montelukast in placebo-controlled pediatric studies and their open-label extensions. *Pediatr Pulmonol.* 2009;44(6):568-579.

Table 1. General characteristics of both montelukast exposed and non-exposed patients.

	Total	**Exposed (400)**	**Non-exposed (400)**	**p-value**
Gender	368M/432F	184M/216F	184M/216F	0.504
Median Age, Q1 - Q3		60, 46 - 68	64, 55.75 - 70	< 0.0001#
Events	37* | 4.6%	5 | 1.25%	32 | 8%	< 0.00001
Mean montelukast exposure		7.83 months		
Residence				
Rural	139 | 17%	108 | 27%	31 | 8%	< 0.00001
Urban	661 | 83%	292 | 73%	369 | 92%	
Educational level				
Low	242 | 30%	68 | 17%	174| 43.5%	< 0.00001
Mid + High	558 | 70%	332 | 83%	226 | 56.5%	
Income				
Low	371 | 46%	175 | 44%	196| 49%	0.08
Mid + High	429 | 54%	225 | 56%	204 | 51%	
Drug prescription				
Antihypertensive	399 | 49.9%	198 | 49.5%	201 | 50.25%	0.89
Antiplatelet	59 |7.37%	20 | 5%	39 | 9.75%	0.01
Diuretic	167 | 20.87%	84 | 21%	83 | 20.75%	0.99
Antipsychotic	3 | 0.37%	0	3 | 0.75%	0.25
Antiandrogens	16 | 2%	5 | 1.25%	11 | 2.75	0.21
Antithyroid	7 | 0.875	3 | 0.75%	4 | 1%	0.99
Anti-hypercholesterolemic	132 | 16.5%	58 | 14.5%	74 | 18.5%	0.15
Antihistamines	9 | 1.125%	4 | 1%	5 | 1.25%	0.99
Antipeptics	3 | 0.375%	0	3 | 0.75%	0.24
Antiarrythmics	4 | 0.5%	1 | 0.25%	3 | 0.75%	0.62
Antianemics	2 | 0.25%	0	2 | 0.5%	0.48
Hypoglycemics	49 | 6.125%	20 | 5%	29 | 7.25%	0.24
Antiepileptics	2 | 0.25%	0	0	0.48
Antitumorals	7 | 0.875%	0	7 | 1.75%	0.022
Antibiotics	3 | 0.375%	0	3 | 0,75%	0.25
Antidepressants	1 | 0.125%	0	1 | 0.25	0.99
CV risk	415| 51.87%	206| 51.5%	209| 52.25%	0.89

* Two patients suffered from both MI and IS; # Wilcoxon test; all the other p value refer to Pearson Chi-square test for association.

Table 2. Hazard ratio (HR) for CV events derived from propensity score matching

Caliper	**N. of Patients in each group**	**N. of Events**	**HR**	**95% CI low**	**95% CI up**	**p-value**
0.4	299	24	0.2	0.068	0.585	0.0033
0.3	284	23	0.211	0.072	0.619	0.0046
0.2	**269**	**22**	**0.222**	**0.075**	**0.657**	**0.0065**
0.1	245	20	0.176	0.052	0.602	0.0056

Table 3 . Hazard ratio (HR) for CV events derived from Cox regression model using PS as correction factor.

N. of Patients in each group	N. of Events	HR	95% CI low	95% CI up	p-value
400 (all sample)	37	0.241	0.09	0.644	0.0046
59 (patients taking antiplatelet drug)	37	0.17	0.065	0.438	0.0003

Figures legends

Figure 1 – Box plot of age of patients without CV events (median = 62, 51 Q1 - 68 Q3) vs. patients that suffered an ischemic event (median = 74, 64 Q1 - 77 Q3).

Figure 2 – Event-free survival curves according to montelukast use.

Hosted file

`Figure-new.pptx` available at https://authorea.com/users/338558/articles/465052-montelukast-use-decreases-cardiovascular-events-in-asthmatics