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BLADDER CANCER RISK IN USERS OF SELECTED DRUGS FOR CARDIOVASCULAR DISEASE PREVENTION

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Abstract:	Purpose: To investigate the relation between bladder cancer risk and the use of selected drugs for cardiovascular disease (CVD) prevention, such as aspirin, statins and calcium channel blockers (CCBs). Methods: We analyzed data from a multicentric case-control study conducted in Italy between 2003 and 2014, including 690 bladder cancer cases and 665 hospital controls. Odds ratios (OR) of bladder cancer and corresponding 95% confidence intervals (CI) were estimated using unconditional multiple logistic regression models. Results: The ORs for bladder cancer were 1.21 (95% CI 0.87-1.68) for regular use of aspirin, 0.72 (95% CI 0.54-0.97) for use of any CCBs, and 1.32 (95% CI 0.87-1.99) for use of any statins. A slight inverse association was found with duration of use of CCBs, while no consistent association was found with duration of use, age at first use and frequency for aspirin and statins use and, further, with indication of use for aspirin (as analgesic or for cardiovascular disease prevention) for aspirin. No significant association was found for use of various combinations of drugs, or for use of all drugs combined (OR of 1.23, 95% CI 0.31-4.85).

	Conclusions: Our data indicate the lack of a relevant association between use of selected drugs for CVD prevention and bladder cancer risk, and suggest a potential favourable role for CCBs.
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Bladder cancer risk in users of selected drugs for cardiovascular disease prevention

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ABSTRACT

Purpose: To investigate the relation between bladder cancer risk and the use of selected drugs for cardiovascular disease (CVD) prevention, such as aspirin, statins and calcium channel blockers (CCBs).

Methods: We analyzed data from a multicentric case-control study conducted in Italy between 2003 and 2014, including 690 bladder cancer cases and 665 hospital controls. Odds ratios (OR) of bladder cancer and corresponding 95% confidence intervals (CI) were estimated using unconditional multiple logistic regression models.

Results: The ORs for bladder cancer were 1.21 (95% CI 0.87-1.68) for regular use of aspirin, 0.72 (95% CI 0.54-0.97) for use of any CCBs, and 1.32 (95% CI 0.87-1.99) for use of any statins. A slight inverse association was found with duration of use of CCBs, while no consistent association was found with duration of use, age at first use and frequency for aspirin and statins use and, further, with indication of use for aspirin (as analgesic or for cardiovascular disease prevention) for aspirin. No significant association was found for use of various combinations of drugs, or for use of all drugs combined (OR of 1.23, 95% CI 0.31-4.85).

Conclusions: Our data indicate the lack of a relevant association between use of selected drugs for CVD prevention and bladder cancer risk, and suggest a potential favourable role for CCBs.

KEYWORDS: aspirin; calcium channel blockers; case-control study; bladder cancer; risk factor; statins

INTRODUCTION

With the progressive aging of the population, drugs for primary prevention of cardiovascular disease (CVD) are increasingly prescribed. These include mostly anti-hypertensives, aspirin and statins, frequently used in association. However, their action on carcinogenesis, particularly on the bladder, is not fully understood when used alone or in various combinations. Aspirin use, due to its anti-inflammatory properties, has been inversely related to the risk of various common cancers, including those of the colorectum, oesophagus, stomach, breast, and prostate (1, 2). Statins have anticancer activities in *'in vivo'* and *'in vitro'* studies (3), and meta-analyses of epidemiological studies showed statistically significant reductions of haematological malignancies (4) and prostate cancer (5), and a non significant decreased risk of lung (6), breast (7) and kidney (8) cancers. However, a recent combined analysis of randomized trials showed no material effect of statin on cancer risk (9). Only a few studies have been conducted on the association between antihypertensive agents and cancer risk. Current use of any antihypertensive agents- such as ACE inhibitors, β-blockers, calcium channel blockers (CCBs)- has been associated with a higher risk of breast cancer, with no relation with duration (10).

Specifically for bladder cancer risk, several epidemiological studies have considered the relation with aspirin with inconsistent results, ranging from null (11, 12), to direct (13) or inverse (14) associations. Two recent meta-analyses pooling such results found an overall null association (15, 16). Two other meta-analyses on statin use and bladder cancer risk indicated no increased risk among users (17, 18). The relation between any antihypertensive agents and bladder cancer risk was investigated in an US population case-control study reporting null results (19).

Since control and prevention of CVD generally involves the use of multiple drugs, drug interactions should also be considered. Particularly, statins are metabolized by the cytochrome P450 3A4 to more water-soluble metabolites excreted in either bile and urine. Drugs inhibiting cytochrome P450 3A4 activity, such as CCBs (verapamil, diltiazem and mibefradil), might increase plasma statin levels.

The aim of this paper is to provide further data on the association between use of selected drugs for CVD prevention and bladder cancer risk using data from a case–control study conducted in Italy between 2003 and 2014.

MATERIALS AND METHODS

A case-control study on bladder cancer was conducted between 2003 and 2014 within an established Italian network of collaborating centres, including Aviano (Pordenone) and Milan in northern Italy, and Naples and Catania in southern Italy (20, 21). Cases were 690 patients (595 men and 95 women, median age 67 years; range 25-84 years) with incident transitional cell carcinoma of the bladder cancer admitted to major general hospitals in the study areas. Nearly all bladder cancers were confirmed by histological testing on tumour tissue specimen from biopsy or surgery, and three cases were confirmed by cytology only. Controls were subjects admitted to the same hospitals as cases for a wide spectrum of acute, non-neoplastic conditions, not related to smoking or other known or likely risk factors for bladder cancer. The control group included 690 patients frequency-matched to cases by study centre, sex and 5-year age group. Twenty-five controls were excluded after enrolment because of inappropriate admission diagnosis, thus leaving 665 eligible controls (561 men and 104 women; median age 66 years; range 27-84 years). Overall, 28.9% of controls were admitted for traumas, 22.1% for non-traumatic orthopaedic disorders, 39.3% for acute surgical conditions, and 9.8% for miscellaneous other illnesses. All study subjects signed an informed consent, according to the recommendations of the Board of Ethics of the study hospitals. The proportion of refusal among cases and controls approached was less than 5%.

All participants were interviewed during their hospital stay using a structured questionnaire including information on sociodemographic characteristics, anthropometric measures, selected lifestyle and dietary habits (including tobacco smoking and alcohol drinking), a personal history of selected diseases and drug use, and family history of cancer. Information on use of aspirin, CCBs and statins included age at first use, frequency and duration of use. Indication for use of aspirin (i.e., analgesic or CVD prevention) was also recorded. Regular use was defined as use at least once a week for more than 6 months. Comprehensive lists of the main preparations in Italy containing aspirin (any medication containing acetyl salicylic acid), CCBs or statins were supplied to facilitate recall.

Odds ratios (ORs) of bladder cancer and the corresponding 95% confidence intervals (CIs) according to the use of aspirin, CCBs and statins were estimated using unconditional multiple logistic regression models adjusted for age, sex, study centre, year of interview, education, tobacco smoking and diabetes. Additional models including further terms for alcohol consumption, body mass index, family history of bladder cancer and history of cystitis did not substantially changed the OR, and therefore these covariates were not included in the final models. ORs of bladder cancer for use of various combinations of the three classes of medications were also estimated.

RESULTS

Table 1 provides the distribution of bladder cancer cases and controls according to selected variables. By design, cases and controls had a similar distribution by study centre, sex, and age. The two groups were also similar in terms of education, whereas current and heavy tobacco smoking was more frequent among cases than controls.

Table 2 shows ORs and 95% CIs of bladder cancer with various measures of use of aspirin, CCBs and statins. A total of 125 cases (18.1%) and 84 controls (12.6%) reported regular use of aspirin, corresponding to an adjusted OR of 1.21 (95% CI 0.87-1.68). The ORs were 1.19 (95% CI 0.75-1.87) for <5 and 1.20 (95% CI 0.78-1.84) for ≥5 years of use and 1.26, (95% CI 0.79-2.02) for patients starting use when aged <60 years and 1.15 (95% CI 0.75-1.75) at age ≥60 years. The ORs were 0.64 (95% CI 0.28-1.46) for use <7 and 1.35 (95% CI 0.95-1.92) for ≥7 times per week, and 0.95 (95% CI 0.39-2.32) for use as an analgesic and 1.29 (95% CI 0.91-1.83) for CVD prevention. As for CCBs, the ORs were 0.72 (95% CI 0.54-0.97) for regular compared with non regular use. The ORs were 0.96 (95% CI 0.64-1.43) for use <7 years and 0.55 (95% CI 0.37-0.82) for use ≥7 years, 0.55 (95% CI 0.37-0.83) in patients starting use when aged <60 years and 0.93 (95% CI 0.63-1.37) in those starting after, and 0.46 (95% CI 0.20-1.06) for <7 and 0.76 (95% CI 0.56-1.04) for >7 times per week. For regular versus never use of statins the OR was 1.32 (95% CI, 0.87-1.99); the OR was lower for <5 year use (OR 0.88, 95% CI 0.48-1.62) than for ≥5 years (OR 1.91, 95% CI 1.09-3.35), and the ORs were 1.83 (95% CI 0.98-3.40) in patients starting use when aged <60 years and 1.05 (95% CI 0.61-1.79) ≥60 years, and 2.26 (95% CI 0.46-11.1) for use <7 and 1.26 (95% CI 0.80-1.91) ≥7 times per week.

Table 3 presents results for combined use of aspirin, any CCBs and any statins. None of the combination was significantly associated with bladder cancer risk, and compared to subjects who did not regularly use any of the three classes of medications; patients using all classes of drugs had an ORs of 1.23 (95% CI 0.31-4.85), although the estimate was based on 7 cases and 4 controls.

DISCUSSION

Data from this Italian study indicate that regular use of selected classes of drugs for CVD prevention (i.e. aspirin, CCBs and statins) doesn't increase bladder cancer risk. The slightly non significant increased risk found for use of aspirin and statins was not supported by the dose- and duration relationships. The significantly decreased risk associated with CCB regular use was consistent with the inverse association with duration of use, but not with frequency of use.

For aspirin use, no association was found also for high cumulative doses in a Spanish case-control study (22), for dose in a New England case-control study (11), for long duration of use (>11 years) in the same study and in the Cancer Prevention Study II Nutrition

Cohort (≥5 years) (23), and for dose and frequency of use in the The Health Professionals Follow-Up Study (24). Moreover, a large-scale, long-term trial based on data from the Women's Health Study showed that low-dose aspiring use (100 mg/day) for an average 10 years did not reduce the incidence of bladder cancer (25). Thus, overall evidence indicates a lack of role of aspirin on bladder carcinogenesis.

The relation of long-term statin use (mostly >5 years) and bladder cancer was considered in several randomized clinical trials, cohort and case-control studies finding mixed results. A meta-analysis of these studies reported an overall relative risk of 1.21 (95% CI 0.92-1.59) (18). Thus, although a few studies (26-28), including ours, found a slight increased risk, overall no association emerged and the issue needs to be further investigated.

To our knowledge, this is the first epidemiological study evaluating the relation between the risk of bladder cancer in CCB users and in users of various combinations of aspirin, statins and CCBs. The inverse association with the dose- and duration of CCB use suggests a real favourable effect on bladder cancer risk. Preclinical studies in 'in vitro' and 'in vivo' have indicated that CCBs may be effective in blocking abnormal cell proliferation in several tumors (29). Anyway, the protective effect of CCB use and bladder cancer in humans needs to be further investigated.

Although based on a relatively large sample size, our study included a small proportion of regular drug users, according to the reported pattern of aspirin use in Italy (30). Moreover, a limitation is that we had no information on the type of medication and the doses. Another possible limitation of our study is selection bias. However, cases and controls came from comparable catchment areas, and the participation rate was almost complete. Another potential limitation is that some of the diagnostic categories of the controls may be associated with increased drug use, mainly aspirin and/or other analgesics. However, the risk estimates did not change across the major diagnostic categories of controls, and patients admitted to hospital for CVD, and diseases

related with smoking were excluded. As for recall bias, hospital controls are preferable with reference to reliability and validity of information on drug use, as they are similarly sensitized towards various aspects of their medical history (31). Major confounding is also unlikely, because the risk estimates were adjusted for major risk factors of bladder cancer, mainly smoking, and further adjustment for many other variables did not modify the risk estimates.

Thus, our findings, although based on few regular users of the selected drugs, are reassuring, suggesting a lack of relationship of aspirin and statins and a potential favourable effect of CCBs used for CVD prevention and bladder cancer risk.

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REFERENCES

1. Bosetti C, Rosato V, Gallus S, Cuzick J, La Vecchia C. (2012) Aspirin and cancer risk: a quantitative review to 2011. Ann Oncol. 23: 1403-15.
2. Cuzick J, Thorat MA, Bosetti C, et al. (2015) Estimates of benefits and harms of prophylactic use of aspirin in the general population. Ann Oncol. 26: 47-57.
3. Coogan PF, Rosenberg L, Strom BL. (2007) Statin use and the risk of 10 cancers. Epidemiology. 18: 213-9.
4. Yi X, Jia W, Jin Y, Zhen S. (2014) Statin use is associated with reduced risk of haematological malignancies: evidence from a meta-analysis. PLoS One. 9: e87019.
5. Bansal D, Undela K, D'Cruz S, Schifano F. (2012) Statin use and risk of prostate cancer: a meta-analysis of observational studies. PLoS One. 7: e46691.
6. Wang J, Li C, Tao H, et al. (2013) Statin use and risk of lung cancer: a meta-analysis of observational studies and randomized controlled trials. PLoS One. 8: e77950.
7. Undela K, Srikanth V, Bansal D. (2012) Statin use and risk of breast cancer: a meta-analysis of observational studies. Breast Cancer Res Treat. 135: 261-9.
8. Zhang XL, Liu M, Qian J, et al. (2014) Statin use and risk of kidney cancer: a meta-analysis of observational studies and randomized trials. Br J Clin Pharmacol. 77: 458-65.
9. Collins R, Reith C, Emberson J, et al. (2016) Interpretation of the evidence for the efficacy and safety of statin therapy. Lancet.
10. Chang CH, Chiang CH, Yen CJ, Wu LC, Lin JW, Lai MS. (2016) Antihypertensive agents and the risk of breast cancer in women aged 55 years and older: a nested case-control study. J Hypertens. 34: 558-66; discussion 66.
11. Baris D, Karagas MR, Koutros S, et al. (2013) Nonsteroidal anti-inflammatory drugs and other analgesic use and bladder cancer in northern New England. Int J Cancer. 132: 162-73.
12. Daugherty SE, Pfeiffer RM, Sigurdson AJ, et al. (2011) Nonsteroidal antiinflammatory drugs and bladder cancer: a pooled analysis. Am J Epidemiol. 173: 721-30.
13. Ratnasinghe LD, Graubard BI, Kahle L, Tangrea JA, Taylor PR, Hawk E. (2004) Aspirin use and mortality from cancer in a prospective cohort study. Anticancer Res. 24: 3177-84.
14. Castelao JE, Yuan JM, Gago-Dominguez M, Yu MC, Ross RK. (2000) Non-steroidal anti-inflammatory drugs and bladder cancer prevention. Br J Cancer. 82: 1364-9.
15. Bosetti C, Rosato V, Gallus S, La Vecchia C. (2012) Aspirin and urologic cancer risk: an update. Nat Rev Urol. 9: 102-10.
16. Zhang H, Jiang D, Li X. (2013) Use of nonsteroidal anti-inflammatory drugs and bladder cancer risk: a meta-analysis of epidemiologic studies. PLoS One. 8: e70008.
17. Luo Y, She DL, Xiong H, Fu SJ, Yang L. (2015) The Prognostic Effect of Statin Use on Urologic Cancers: An Updated Meta-Analysis of 35 Observational Studies. Medicine (Baltimore). 94: e1523.
18. Zhang XL, Geng J, Zhang XP, et al. (2013) Statin use and risk of bladder cancer: a meta-analysis. Cancer Causes Control. 24: 769-76.
19. Jiang X, Castelao JE, Yuan JM, et al. (2010) Hypertension, diuretics and antihypertensives in relation to bladder cancer. Carcinogenesis. 31: 1964-71.
20. Polesel J, Bosetti C, di Maso M, et al. (2014) Duration and intensity of tobacco smoking and the risk of papillary and non-papillary transitional cell carcinoma of the bladder. Cancer Causes Control. 25: 1151-8.
21. Turati F, Polesel J, Di Maso M, et al. (2015) Diabetes mellitus and the risk of bladder cancer: an Italian case-control study. Br J Cancer. 113: 127-30.
22. Fortuny J, Kogevinas M, Garcia-Closas M, et al. (2006) Use of analgesics and nonsteroidal anti-inflammatory drugs, genetic predisposition, and bladder cancer risk in Spain. Cancer Epidemiol Biomarkers Prev. 15: 1696-702.
23. Jacobs EJ, Thun MJ, Bain EB, Rodriguez C, Henley SJ, Calle EE. (2007) A large cohort study of long-term daily use of adult-strength aspirin and cancer incidence. J Natl Cancer Inst. 99: 608-15.
24. Genkinger JM, De Vivo I, Stampfer MJ, Giovannucci E, Michaud DS. (2007) Nonsteroidal antiinflammatory drug use and risk of bladder cancer in the health professionals follow-up study. Int J Cancer. 120: 2221-5.
25. Cook NR, Lee IM, Gaziano JM, et al. (2005) Low-dose aspirin in the primary prevention of cancer: the Women's Health Study: a randomized controlled trial. JAMA. 294: 47-55.
26. Friedman GD, Flick ED, Udaltsova N, Chan J, Quesenberry CP, Jr., Habel LA. (2008) Screening statins for possible carcinogenic risk: up to 9 years of follow-up of 361,859 recipients. Pharmacoepidemiol Drug Saf. 17: 27-36.

27. Sato S, Ajiki W, Kobayashi T, Awata N, Group PCSS. (2006) Pravastatin use and the five-year incidence of cancer in coronary heart disease patients: from the prevention of coronary sclerosis study. J Epidemiol. 16: 201-6.
28. Vinogradova Y, Coupland C, Hippisley-Cox J. (2011) Exposure to statins and risk of common cancers: a series of nested case-control studies. BMC Cancer. 11: 409.
29. Mason RP. (1999) Calcium channel blockers, apoptosis and cancer: is there a biologic relationship? J Am Coll Cardiol. 34: 1857-66.
30. Lugo A, Asciutto R, Bosetti C, Parazzini F, La Vecchia C, Gallus S. (2014) Regular use of aspirin for cardiovascular disease prevention in Italy. Prev Med. 63: 48-51.
31. Bosetti C, Tavani A, Negri E, Trichopoulos D, La Vecchia C. (2001) Reliability of data on medical conditions, menstrual and reproductive history provided by hospital controls. J Clin Epidemiol. 54: 902-6.

Table 1. Distribution of 690 cases of bladder cancer and 665 controls according to centre, sex, age and other selected variables. Italy, 2003-2014.

	Cases		Controls		p value[b]
	No.	%	No.	%	
Centre					
Pordenone	242	35.1	250	37.6	
Milan	241	34.9	238	35.8	
Naples	129	18.7	100	15.0	
Catania	78	11.3	77	11.6	0.34
Sex					
Men	595	86.2	561	84.4	
Women	95	13.8	104	15.6	0.33
Age (years)					
< 60	148	21.5	178	26.8	
60-64	107	15.5	119	17.9	
65-69	164	23.8	147	22.1	
70-74	155	22.5	124	18.7	
≥ 75	116	16.8	97	14.6	0.06
Education (years)[a]					
< 7	292	42.4	273	41.1	
7 - 11	224	32.5	215	32.3	
≥ 12	173	25.1	177	26.6	0.80
Tobacco smoking[a]					
Never smokers	96	14.1	237	35.6	
Ex-smokers	310	45.5	284	42.7	
Current smokers					
< 15 cigarettes/day	79	11.6	53	8.0	
15-24 cigarettes/day	127	18.7	68	10.2	
≥ 25 cigarettes/day	69	10.1	23	3.5	<0.001
Diabetes					
No	578	83.8	608	91.4	
Yes	112	16.2	57	8.6	<0.001

[a]The sum does not add up to the total because of some missing values.
[b] p-value for association from $\chi 2$ statistic.

Table 2. Distribution of 690 bladder cancer cases and 665 controls, with corresponding odds ratio (OR) and 95% confidence interval (CI), according to aspirin[a], calcium channel blockers (CCBs)[a] and statin[a] use. Italy, 2003–2014.

	Cases (%)	Controls (%)	OR[b] (95% CI)
Aspirin[a] use			
Non regular users	564 (81.9)	581 (87.4)	1.00[c]
Regular users	125 (18.1)	84 (12.6)	1.21 (0.87-1.68)
Duration of use (years)			
<5	58 (8.4)	39 (5.9)	1.19 (0.75-1.87)
≥5	65 (9.5)	45 (6.8)	1.20 (0.78-1.84)
χ^2-trend (p-value)			1.0 (0.3175)
Age at first use (years)			
<60	57 (8.3)	35 (5.3)	1.26 (0.79-2.02)
≥60	67 (9.7)	49 (7.4)	1.15 (0.75-1.75)
Frequency of use (times/week)			
<7	13 (1.9)	14 (2.1)	0.64 (0.28-1.46)
≥7	112 (16.3)	69 (10.4)	1.35 (0.95-1.92)
χ^2-trend (p-value)			2.3 (0.1287)
Indication			
Analgesic	13 (1.9)	14 (2.1)	0.95 (0.39-2.32)
Cardiovascular prevention	112 (16.3)	69 (10.4)	1.29 (0.91-1.83)
CCB use[a]			
Non regular users	556 (80.8)	515 (77.4)	1.00[c]
Regular users	132 (19.2)	150 (22.6)	0.72 (0.54-0.97)
Duration of use (years)			
<7	70 (10.2)	65 (9.8)	0.96 (0.64-1.43)
≥7	60 (8.7)	83 (12.5)	0.55 (0.37-0.82)
χ^2-trend (p-value)			7.5 (0.0061)
Age at first use (years)			
<60	54 (7.8)	79 (11.9)	0.55 (0.37-0.83)
≥60	78 (11.3)	71 (10.7)	0.93 (0.63-1.37)
Frequency of use (times/week)			
<7	12 (1.7)	15 (2.3)	0.46 (0.20-1.06)
≥7	119 (17.3)	134 (20.2)	0.76 (0.56-1.04)
χ^2-trend (p-value)			3.4 (0.0640)
Statin use[a]			
Non regular users	618 (89.7)	615 (92.5)	1.00[c]
Regular users	71 (10.3)	50 (7.5)	1.32 (0.87-1.99)
Duration of use (years)			
<5	25 (3.6)	27 (4.1)	0.88 (0.48-1.62)
≥5	46 (6.7)	22 (3.3)	1.91 (1.09-3.35)
χ^2-trend (p-value)			3.8 (0.0525)
Age at first use (years)			
<60	31 (4.5)	20 (3.0)	1.83 (0.98-3.40)
≥60	40 (5.8)	29 (4.4)	1.05 (0.61-1.79)
Frequency of use (times/week)			
<7	8 (1.2)	2 (0.3)	2.26 (0.46-11.1)
≥7	63 (9.1)	48 (7.2)	1.26 (0.82-1.94)
χ^2-trend (p-value)			1.4 (0.2315)

[a] The sum does not add up to the total because of some missing values. [b] Estimated from multiple logistic regression model adjusted for age, sex, study centre, year of interview, education, tobacco smoking and diabetes. [c] Reference category.

Table 3. Distribution of 690 bladder cancer cases and 665 controls, with corresponding odds ratio (OR) and 95% confidence interval (CI), according combined use of aspirin[a], calcium channel blockers (CCBs)[a], and statins[a]. Italy, 2003–2014.

	Cases (%)	Controls (%)	OR[b] (95% CI)
Combined use of aspirin, CCBs and statins			
No	440 (64.0)	440 (66.2)	1.00[c]
Only aspirin	65 (9.4)	46 (6.9)	1.16 (0.75-1.79)
Only statins	29 (4.2)	18 (2.7)	1.59 (0.82-3.09)
Only CCBs	82 (11.9)	106 (15.9)	0.77 (0.54-1.10)
Aspirin + statins	22 (3.2)	11 (1.7)	1.90 (0.88-4.12)
Aspirin + CCBs	30 (4.4)	23 (3.5)	0.79 (0.43-1.45)
Statins + CCBs	13 (1.9)	17 (2.6)	0.59 (0.27-1.32)
All drugs	7 (1.0)	4 (0.6)	1.23 (0.31-4.85)

[a] The sum does not add up to the total because of some missing values.
[b] Estimated from multiple logistic regression model adjusted for age, sex, study centre, year of interview, education, tobacco smoking and diabetes.
[c] Reference category.