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Use of fluorquinolones is associated with a reduced risk of coronary heart disease in diabetes mellitus type 2 patients

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Aims The aim of the present study was to investigate whether use of specific antibiotic drugs decreases the risk of coronary heart disease in diabetes mellitus type 2 patients.

Methods and Results Data were obtained from the PHARMO Record Linkage System comprising pharmacy records and hospitalizations for all 450 000 residents of eight Dutch cities. In a nested case-control study among diabetes mellitus type 2 patients, 244 cases with a first hospitalization for coronary heart disease and 686 controls without coronary heart disease matched on age, sex, calendar time, and registration date in PHARMO RLS were selected. Use of antibiotic drugs among cases and controls was determined over 3 years prior to the event. Use of fluorquinolones for more than 14 days compared to no use of fluorquinolones was associated with a lower risk of coronary heart diseases (OR_{adj}=0·30 (95%CI: 0·12–0·75)). No association between tetracycline, macrolide and lincosamide treatment, or other antibiotic drugs (penicillins, cephalosporines, sulphonamides and trimethoprim), and the risk of coronary heart disease was found.

Conclusion Our results suggest that treatment with fluorquinolones in doses commonly prescribed in routine clinical practice is associated with a reduction in the risk of coronary heart diseases among diabetes mellitus type 2 patients.
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Key Words: Antibiotic drugs, coronary heart disease, diabetes mellitus type 2, epidemiology.

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Introduction

Although there is increasing evidence from several observational studies[1–11] and clinical trials[5,12–14] that certain bacterial infections may play a role in the aetiology of coronary heart disease, the underlying mechanism remains unclear. *Chlamydia pneumoniae* infections, in particular, are thought to contribute to the development of atherosclerosis. If such a causal association exists, it may be expected that subjects who used antibiotics active against the bacteria, regardless of indication, might be at lower risk of developing coronary heart disease than subjects who did not use antibiotic drugs.

In a previous study[10], it was reported that an association between fluorquinolones and the risk of acute myocardial infarction was found, but not between tetracyclines and macrolides, and the risk of myocardial infarction despite their antibacterial activity against *Chlamydia pneumoniae*. The effect of fluorquinolones on atherosclerosis may therefore be mediated via their non-bacterial inhibitory actions, i.e. their stabilizing effect on the cytoskeleton of endothelium cells[15] and their effect on chondrocytes in humans[16], because calcification plays a major role in the later stages of plaque formation in atherosclerosis[17].

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This effect may be even more visible in diabetes mellitus patients since they are thought to be more susceptible to infections as well as to atherosclerosis[18–20]. Studies so far have excluded diabetes mellitus patients[10,11] or did not report results of diabetes mellitus patients separately or did not include all antibiotic drug classes[21].

The aim of the present study was to investigate whether use of antibiotic drugs decreases the risk of coronary heart disease in diabetes mellitus type 2 patients, and whether these effects are specific for fluorquinolones.

Methods

Study setting

The PHARMO Record Linkage System (PHARMO RLS) was used as a data source for this study. PHARMO RLS comprizes pharmacy drug-dispensing records linked to hospital admission data of all community-dwelling residents of eight Dutch cities, counting for more than 450 000 patients histories, from 1985 onwards[22]. Virtually complete data from this cohort covering a period from 1985–1998 were available for each subject including sex, date of birth, drug names with anatomical therapeutic chemical codes, dispensing date, total supply, dosage regimen, prescriber, and hospital discharge diagnoses. Using data on supply and dosage regimen, duration of exposure could be estimated. Drugs were coded according to the Anatomical Therapeutic Chemical (ATC) classification. Hospital diagnoses were coded according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM codes).

Study subjects

Diabetes mellitus type 2 patients were defined as subjects in whom oral antidiabetic therapy was initiated between 1985 and 1998. Diabetes mellitus type 2 patients were included in the cohort if they received at least two prescriptions of oral antidiabetic drugs and no insulin or analogues before the date of starting oral antidiabetic therapy (n=12 140).

In this cohort, a nested case-control study was performed by selecting patients with a first hospitalization for coronary heart disease and with a PHARMO RLS registration of at least 3 years before the date of the hospitalization for coronary heart disease. The 3-year period was chosen to allow us to identify a minimum period of exposure comparable with the studies of Meier *et al.*[11] and Herings *et al.*[10]. An index date was assigned to each subject. For the cases, the index date was the date of the first hospitalization for coronary heart disease; for controls, the index date was identical to the index date of the case within the same case-control pair. Coronary heart disease was defined as ischaemic heart diseases (ICD-9-CM codes 410-414), including myocardial infarction (ICD-9-CM codes 410) and angina pectoris (ICD-9-CM codes 413).

For each case, we identified up to five controls from the cohort of diabetes type 2 patients without an atherosclerotic coronary event who were matched on age (year of birth), sex, calendar time and same date of first entry into the PHARMO RLS system ($\pm$ 50 days). We excluded all subjects who were admitted to the hospital for stroke (ICD-9-CM codes 430-438) before the index date.

Exposure to antibiotic drugs

Previous use of antibiotic drugs among cases and controls was determined for the 3 years preceding the index date[10,11]. Antibiotic drug use was classified into the following classes: tetracyclines, penicillins, cephalosporins, sulphonamides and trimethoprim, macrolides and lincosamides, and (fluoro)quinolones. For the analyses, penicillins, cephalosporins and sulphonamides and trimethoprim were grouped together as 'other antibiotic drugs'. Defined daily doses (DDD) were calculated to determine the duration of exposure to antibiotic drugs. The DDD is a technical measurement unit giving the assumed average daily maintenance dose for an adult for the main indication. The total duration of therapy with these drugs was calculated by using the sum of the quantities dispensed during the study period. Exposure to antibiotic drugs was categorized as 0, 1–14 (short term use), and >14 days (long term use) of cumulative drug use. Fourteen days of antibiotic drug use roughly corresponds with two courses of antibiotic drugs.

Data analysis

Conditional logistic regression was performed to estimate matched odds ratios (OR) and 95% confidence intervals (CI) using EGRET[23].

Potential confounders that could be assessed by using pharmacy and hospitalization data included age, sex, calendar year, use of antiasthmatic drugs, cardiovascular drug use (e.g. cardiac drugs, diuretics, beta-blockers, calcium-channel blockers, ACE inhibitors, lipid lowering agents, antithrombotic drugs), hormone replacement therapy, hospitalization for hypertension and comorbidity as measured by the chronic disease score. The chronic disease score (CDS) was calculated by assigning scores (0–5) to classes of drugs according to the severity of the disease for which they were prescribed during the year before the index date[24,25].

Results

We identified 244 cases and 686 matched controls in the period from 1985 to 1998. General characteristics are

Table 1 General characteristics of the study population

Characteristic	Cases (%) n=244	Controls (%) n=686
Mean age†	66·9 (0·7)	67·3 (0·4)
Male	54·4	52·9
Mean registration in PHARMO†‡	8·4 (0·2)	8·9 (0·1)*
Mean duration of DM2†§	3·5 (0·2)	3·0 (0·1)*
Co-morbidity		
Antiasthmatic drugs	26·6	24·1
Hormone replacement therapy	11·1	8·2
Cardiac drugs	53·3	27·4*
Diuretics	51·2	42·0*
Beta-blockers	58·6	36·6*
Calcium channel blockers	45·1	24·3*
ACE inhibitors¶	34·8	28·9
Lipid lowering drugs	16·4	11·7
Antithrombotic drugs	51·6	29·0*
Chronic disease score		
0	13·9	26·5*
1–2	7·0	11·4
>2	79·1	62·1*

*χ2-test ($P<0·05$) for comparison of proportions and Students t-test ($P<0·05$) for comparison of means between cases and controls.
†Years with standard error of the mean in parentheses.
‡Registration duration in PHARMO until index date.
§Duration of diabetes mellitus type 2 (DM2) (defined as the first oral antidiabetic drug therapy) until the index date.
¶ACE inhibitors=angiotensin converting enzyme inhibitors.

shown in Table 1. The mean age (±SEM) was 66·9 ± 0·7 years in cases and 67·3 ± 0·4 years in controls, and about 54·4% of the cases and 52·9% of the controls were male. Cases and controls were not different with respect to treatment for respiratory complaints (antiasthmatic drugs), hormone replacement therapy, treatment with ACE inhibitors and lipid lowering drugs. The mean duration of known presence of diabetes mellitus type 2 was longer in cases than controls. Furthermore, treatment with cardiac drugs, diuretics, beta-blockers, calcium channel blockers, antithrombotic drugs was more common in cases than in controls. The prevalence of chronic diseases (by using the CDS) was more manifest in cases than in controls.

Cumulative treatment of more than 14 days with fluorquinolones compared to no use of fluorquinolones was associated with a lower risk of coronary heart diseases (OR_{adj}=0·30 (95%CI: 0·12–0·75)) (Table 2). No association between the duration of prescribed treatment of tetracyclines, macrolides and lincosamides, other antibiotic drugs, or all categories combined, with the risk of coronary heart diseases was found. When restricting the analysis to cases of acute myocardial infarction (AMI) (90 cases and 252 controls) only, a similar trend between the cumulative use of fluorquinolones and the risk of AMI was found ($OR_{adj\ 1–14\ days}$=2·91 (95%CI: 0·94–9·04) and $OR_{adj\ >14\ days}$=0·15 (95%CI: 0·02–1·23)).

When including cases with hospitalizations for other ischaemic heart diseases (ICD-9-CM code 413-414) (154 cases and 434 controls) only, again subjects who received more than 14 days of fluorquinolones in the 3 years prior to the index date were at a reduced risk of developing other ischaemic heart diseases ($OR_{adj\ 1–14\ days}$=0·60 (95%CI: 0·23–1·58) and OR_{adj} >14 days=0·29 (95%CI: 0·10–0·88)).

The association between fluorquinolone use and the risk of coronary heart disease was similar in males ($OR_{adj\ 1–14\ days}$=1·31 (95%CI: 0·47–3·67) and $OR_{adj\ >14\ days}$=0·25 (95%CI: 0·07–0·93)) and females ($OR_{adj\ 1–14\ days}$=1·14 (95%CI: 0·46–2·83) and $OR_{adj\ >14\ days}$=0·40 (95%CI: 0·10–1·53)) compared with no use of fluorquinolones. The results were consistent

Table 2 Hospitalization for coronary heart diseases and cumulative use of selected antibiotic drugs

Antibiotic drug	Cumulative days of treatment	Cases n=244 No. (%)	Controls n=686 No. (%)	OR crude	95% CI	OR_{adj}	95% CI
Any antibiotic drug	0	96 (39·3)	310 (45·2)	1·00	reference	1·00	reference
	1–14	55 (22·5)	161 (23·5)	1·11	0·75–1·63	0·96	0·62–1·49
	>14	93 (38·1)	215 (31·3)	1·31	0·91–1·87	0·97	0·64–1·49
Tetracyclines	0	176 (72·1)	515 (75·1)	1·00	reference	1·00	reference
	1–14	44 (18·0)	97 (14·1)	1·26	0·84–1·90	0·99	0·63–1·56
	>14	24 (9·8)	74 (10·8)	0·93	0·56–1·54	0·76	0·43–1·35
Macrolides and lincosamides	0	214 (87·7)	629 (91·7)	1·00	reference	1·00	reference
	1–14	22 (9·0)	44 (6·4)	1·54	0·89–2·67	1·22	0·68–2·20
	>14	8 (3·3)	13 (1·9)	1·83	0·73–4·55	1·60	0·60–4·29
Fluorquinolones	0	218 (89·3)	612 (89·2)	1·00	reference	1·00	reference
	1–14	20 (8·2)	37 (5·4)	1·46	0·80–2·64	1·13	0·57–2·23
	>14	6 (2·5)	37 (5·4)	0·40	0·16–0·99	0·30	0·12–0·75
Other antibiotic drugs	0	128 (52·5)	404 (58·9)	1·00	reference	1·00	reference
	1–14	57 (23·4)	156 (22·7)	1·17	0·80–1·70	1·08	0·71–1·66
	>14	59 (24·2)	126 (18·4)	1·37	0·93–2·03	1·02	0·65–1·61

OR=odds ratio; CI=confidence interval; OR_{adj}=adjusted odds ratio for hospitalizations for hypertension, use of antiasthmatic drugs, cardiac drugs, miscellaneous antihypertensive drugs, diuretics, beta-blockers, calcium channel blockers, ACE inhibitors, lipid lowering drugs, antithrombotic drugs, and chronic disease score.

across age strata with an $OR_{adj\ 1–14\ days}$ of 0·90 (95%CI: 0·22–3·64) and $OR_{adj\ >14\ days}$ of 0·41 (95%CI: 0·11–1·55) for subjects aged ≤65 years and with an $OR_{adj\ 1–14\ days}$ of 1·10 (95%CI: 0·50–2·42) and $OR_{adj\ >14\ days}$ of 0·12 (95%CI: 0·03–0·57) for subjects aged >65 years.

Discussion

In this study among diabetes mellitus type 2 patients, the use of fluorquinolones was associated with a reduced risk of coronary heart disease. This association was in concordance with Meier *et al*.[11] and Herings *et al*.[10] who investigated the association in relation to myocardial infarction only and in a population without diabetes mellitus type 2 patients. However, the risk reduction occurred for long term use (>14 days), but not for short term use (≤14 days). Although diabetes mellitus type 2 patients have a higher absolute risk of cardiovascular diseases and may be more susceptible to infections[18,19], no difference in the association between antibiotic drug use, in particular fluorquinolone use, and coronary heart diseases was observed compared to previous studies that excluded diabetes mellitus patients[10,11]. The finding that use of fluorquinolones is associated with a lower risk for coronary heart disease may be explained by infections with organisms susceptible to quinolones being involved in the aetiology of ischaemic heart disease. However, our results are not completely compatible with an inhibitory effect on *Chlamydia pneumoniae,* as no association was found for tetracyclines and macrolides. Tetracyclines and macrolides have substantial antibacterial activity against *Chlamydia pneumoniae*[26], whereas quinolones have antibacterial activity against *Chlamydia pneumoniae* in vitro[26,27], but their efficacy in vivo has so far been poorly established. A positive effect of macrolides on cardiovascular diseases has been reported repeatedly[5,12,13,28,29]. In the study of Neumann *et al*. however, the protective effect of a prolonged roxithromycin course was limited to those patients who had elevated antibody titres against *Chlamydia pneumoniae*[29]. Both newer macrolides and fluorquinolones are more effective against *Chlamydia pneumoniae* than erythromycin and ciproxin, respectively.

The absence of an effect of sulphonamides, cephalosporins and penicillins on coronary heart diseases is in agreement with the ineffectiveness of these antibiotic drugs against *Chlamydia pneumoniae*[26] and with the results from the previous studies on antibiotic drug use and the risk of myocardial infarction[10,11,30].

Courses of treatment in antibiotic intervention studies for coronary heart diseases are for at least 1 month and usually 3 months[5,12–14]. In this sense, the usual antibiotic drug courses are too short. More than one course of fluorquinolones was demanded in this study. In the study by Herings *et al*.[10], high doses were defined as standard dose courses of longer than 6 days. These doses were chosen as effective for the eradication of *Chlamydia pneumoniae.* Tetracyclines, and macrolides, in particular, were not associated with a lower risk of AMI when given in high doses or multiple courses during a sufficient period of time. These results are consistent with those of Jackson *et al*.[21].

However, before the first cardiac event, the pathogen possibly present in lesions might be in a chronic state and, therefore, not vulnerable to antibiotic drugs that effect on protein synthesis. Alternatively, as regards chronic *Chlamydia pneumoniae* infections, a recent study suggested that, although the pathogen does not multiply, nucleic acid synthesis is going on[31]. A drug active in this metabolic stage, such as a fluorquinolone, might well be effective. A large ongoing study, PROVE IT, using gatifloxacin is studying this possibility and may give more insight into this mechanism.

Alternatively, the effects of fluorquinolones may be mediated through their non-bacterial inhibitory actions. Fluorquinolones have been reported to stabilize the cytoskeleton of endothelium cells[15] and may have an effect on chondrocytes in humans[16], and calcification plays a major role in the later stages of plaque formation in atherosclerosis[17,32]. Moreover, because we observed a protective effect over a period as short as 3 years, this may reflect prevention of plaque rupture or thrombosis rather than prevention of atherosclerosis per se[33].

A limitation of this study is the lack of information on certain prognostic factors, such as body mass index and smoking history. However, it is doubtful that the choice of antibiotic drug prescription was influenced by these factors. In addition, socio-economic status (SES) has been proposed as a possible confounder[11,34]. However, it seems unlikely that quinolones, as opposed to other antibiotics, were preferentially prescribed to subjects with a high SES and would therefore confound our results, because antibiotics are fully reimbursed by Dutch insurance schemes. However, we cannot rule out confounding due to unknown or unmeasured factors in this observational study.

Patients using antibiotic drugs could have been noncompliant with their therapy and therefore could have used less antibiotic drugs than prescribed. However, this would have led to an underestimation of the association between antibiotic drug use and coronary heart disease.

It must be emphasized that these observational findings should not be interpreted as suggesting that antibiotic drugs, and especially fluorquinolones, should be given to diabetes mellitus type 2 patients to prevent coronary heart diseases[35–38]. These important findings on the preventive potential of fluorquinolones in coronary heart diseases need further confirmation, particularly from large-scale prospective randomized trials.

In conclusion, our results suggest that treatment with fluorquinolones in doses commonly prescribed in routine clinical practice is associated with a reduction in the risk of coronary heart diseases among diabetes mellitus type 2 patients.

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