Original Article

Risk for cardiovascular disease in patients with nontuberculous mycobacteria treated with macrolide

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Background: Macrolide antibiotics are the most important pharmacological agents for the treatment of nontuberculous mycobacterial disease. We investigated the incidence of acute cardiovascular events in patients taking macrolides for nontuberculous mycobacterial disease and determined the difference in risk between clarithromycin and azithromycin.

Methods: A population-based retrospective cohort study was conducted in South Korea using the Health Insurance Review and Assessment Service database. Patients ≥40 years treated with macrolide for nontuberculous mycobacteria (NTM) between 2011 and 2015 were examined. The primary outcome was hospitalization or emergency department visit for cardiovascular disease along with acute myocardial infarction, cerebrovascular disease, and cardiac arrhythmia. The standardized incidence ratio (SIR) for cardiovascular disease was calculated by comparing the patients with the general population in the year 2013. Cox proportional hazard model was used to compare the risk between clarithromycin and azithromycin.

Results: In total, 16,525 patients with nontuberculous mycobacterial disease treated with macrolide were included; 13,870 received clarithromycin and 2,655 received azithromycin. The cardiovascular incidence was significantly higher in patients with nontuberculous mycobacterial disease than in the age- and sex-stratified general population [SIR, 1.44; 95% confidence interval (CI), 1.27–1.61]. The risk was not significantly different between patients treated with clarithromycin and azithromycin (adjusted hazard ratio, 0.90; 95% CI, 0.65–1.24).

Conclusions: The incidence of cardiovascular disease was significantly higher in patients treated with macrolide for nontuberculous mycobacterial disease than in the general population. This risk was not different between patients treated with clarithromycin and azithromycin.

Keywords: Azithromycin; cardiac arrhythmias; cerebrovascular disease; clarithromycin; myocardial infarction

Submitted Apr 21, 2018. Accepted for publication Sep 25, 2018.
doi: 10.21037/jtd.2018.09.145
View this article at: http://dx.doi.org/10.21037/jtd.2018.09.145

Introduction

The incidence and prevalence of lung disease caused by nontuberculous mycobacteria (NTM) continue to increase around the world (1), including in South Korea (2), making NTM disease an emerging public health threat. Chronic lung infection is the most common form of NTM disease (3). In South Korea, lung disease due to NTM is most frequently caused by *Mycobacterium avium* complex (MAC) (3).

Patients with a history of tuberculosis are at a higher risk for developing cardiovascular disease, such as ischemic

stroke or acute coronary syndrome (4,5). In addition, community-acquired pneumonia is a well-known significant risk factor for inflammation-mediated acute cardiac events (6,7). Considering that majority of patients with NTM disease can present with manifestations that are similar to those of tuberculosis or pneumonia (3,8), it is possible that NTM disease itself is a high risk factor for cardiovascular disease. Moreover, a number of studies have shown an association between increased cardiovascular morbidity and mortality with administration of macrolide (9-13), the core drug for the treatment of NTM disease (3,8). Therefore, the use of macrolide can possibly increase the risk for cardiovascular disease in patients with NTM disease.

Additionally, many studies have reported that the risk for cardiovascular disease is different between patients treated with clarithromycin and azithromycin (14-17), which are the two main macrolides used for the treatment of most NTM species (3,8). Given the similar efficacy (18) and prescription rate (19) between these two drugs, evaluation of the difference in risk for cardiovascular disease between patients treated with these two macrolides would have a clinically significant implication.

To date, no studies have examined these issues. Therefore, we aimed to investigate the incidence of acute cardiovascular events in patients with NTM disease treated with macrolide and identify whether there is a difference in the risk for cardiovascular disease between patients treated with clarithromycin and azithromycin.

Methods

Data sources and ethics

This was a population-based retrospective cohort study that used the Health Insurance Review and Assessment Service (HIRA) database of South Korea. HIRA is a government-affiliated agency that assesses the accuracy of claims for the National Health Insurance, a compulsory system that covers 96.6% of the entire population of 48.6 million, and for the National Medical Aid, which covers 3.5% of the South Korean population (20). The patients' claims data that were submitted by healthcare providers between January 1, 2011 and December 31, 2015 were obtained. The data given by HIRA had anonymized identifiers, according to the Act on the Protection of Personal Information that is maintained by public agencies. All diagnoses were coded using the Korean Classification of Disease, sixth edition, which is a modified version of the International Classification of Disease and Related Health Problems, tenth revision (ICD-10). The database contained longitudinal patient information on demographics, diagnosis, and prescriptions. The prescription data included the drug name, dose, prescription date, and supply days.

This study protocol was approved by the Institutional Review Board of Asan Medical Center, Seoul, South Korea (IRB No. 2016-0880). Informed consent was waived because the study used an existing database that was provided in a de-identified format.

Study subjects, exposure assessment and study outcome

To secure at least 180 days of observation period, patients with NTM disease were chosen between July 1, 2011 and June 30, 2015 from the HIRA database. NTM disease was diagnosed in patients with claims for NTM (ICD-10 A31). Initially, a total of 44,863 patients aged 40 years or older with a diagnosis of NTM were identified from the HIRA database in the study period. Then, we excluded patients who were not prescribed macrolides and those who had been recorded to have ischemic heart disease (ICD-10 I20-5), cerebrovascular disease (ICD-10 I60-9), or cardiac arrhythmia (ICD-10 I44-5, I47-9) before the first prescription of macrolide. Patients who received both rifampin and ethambutol more than once with macrolide were defined to have MAC disease.

The use of macrolide was designated as prescription of clarithromycin or azithromycin. The index date was defined as the date of prescription of the macrolide. Based on previous studies showing a short-term use of clarithromycin was associated with increased cardiovascular mortality for as long as 10 years, (9,10), we assumed that macrolides had a persistent effect on cardiovascular disease even after discontinuation; that is, once a patient with NTM disease has been prescribed macrolide, the patient is regarded to be under the influence of it even after its discontinuation and until the end of the follow-up period (December 31, 2015) (*Figure 1A*). In addition, if one macrolide was subsequently changed into another, the period until the change of the first macrolide was considered as the period of use for that drug and the period of the subsequent macrolide prescription was ignored (*Figure 1B*). Finally, in the case of the study outcome occurred during the use or after discontinuation of the macrolide, the time of onset of the study outcome was defined as the end of the exposure duration (*Figure 1C*).

The primary outcome was the initial and subsequent

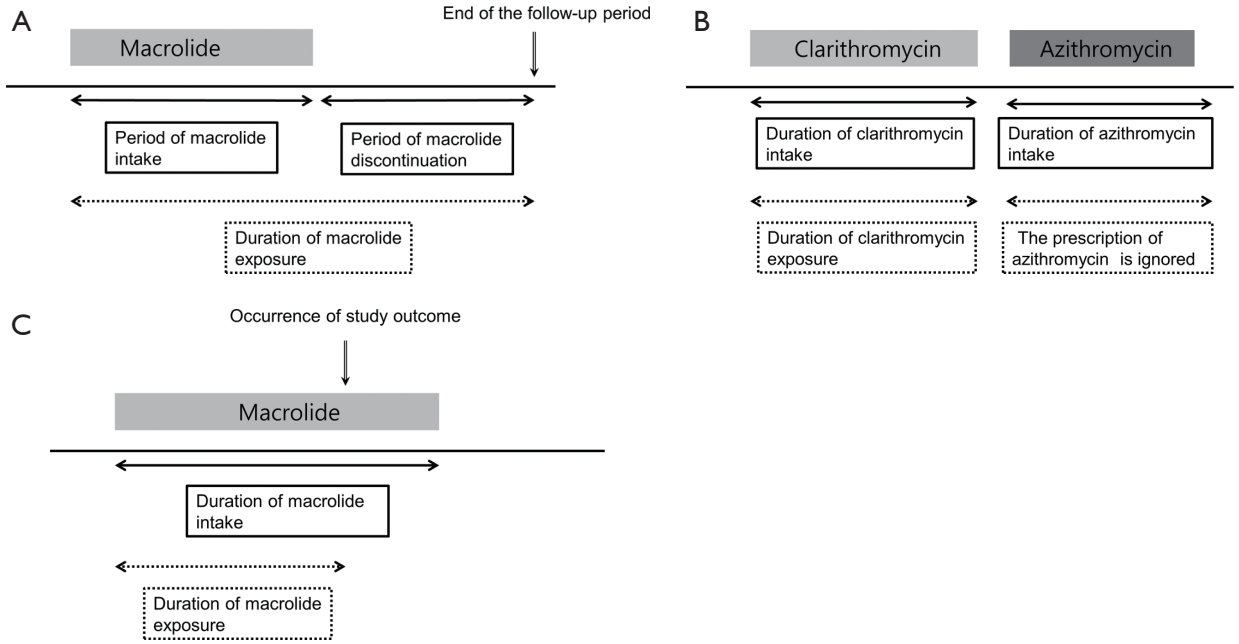

Figure 1 Models for calculating the duration of macrolide exposure. (A) In case of no occurrence of study outcome, the duration of exposure to macrolide was defined as the period until the end of follow-up, including the period of discontinuation; (B) if clarithromycin was initially prescribed and was changed to azithromycin (and *vice versa*), clarithromycin was designated as the prescribed macrolide and the use of subsequent azithromycin was ignored (and *vice versa*); (C) in case of occurrence of study outcome, the duration of macrolide exposure was defined as the period until the date of occurrence of study outcome, regardless of a subsequent macrolide use.

hospitalization or emergency department visit for a diagnosis of cardiovascular disease along with acute myocardial infarction (ICD-10 I21-2), cerebrovascular disease (ICD-10 I60-9), and cardiac arrhythmia (ICD-10 I44-5, I47-9) (9). All patients were followed up until the study outcome occurred, a macrolide was switched, or the end of the follow-up period was reached, whichever came first.

Statistical analyses

Baseline characteristics were presented as numbers with percentages for categorical variables and as mean and standard deviation or median and interquartile range for continuous variables. The covariates selected included age at index date, gender, presence of comorbidities, and pre-existing medications. Comorbidities were identified by ICD-10, all of which were assessed for 180 days prior to the index date. We selected the comorbidities that might influence the risk for cardiovascular disease, with modified details on ICD-10 considering clinical practice (*Table S1*), based on Charlson index (21,22) added to known risk factors (23). The category of pre-existing medications was selected based on previous studies (11,13) (*Table S2*). The concomitant medications for the treatment of NTM disease were determined based on the American Thoracic Society guidelines for NTM treatment (24).

To control the potential confounders in an observational study, inverse probability treatment weights (IPTW) were applied and accounted for the limited number of cardiovascular diseases. IPTW was estimated by propensity score and was derived by logistic regression analysis for assignment to exposure groups using all baseline covariates included in *Table 1*; IPTW was defined as the inverse of (1 – propensity score) for clarithromycin group and as the inverse of the propensity score for the azithromycin group. In order to reduce the influence of outliers, the weights were stabilized by multiplying with the mean propensity score of the given exposure group. Balances in the distribution of the baseline covariates were estimated by the standardized difference between the two groups, before and after IPTW adjustment (25-27).

Table 1 Baseline characteristics of the 16,525 study patients with nontuberculous mycobacterial disease treated with macrolide before and after IPTW adjustment

Characteristics	Unadjusted data			Data adjusted by IPTW		
	Clarithromycin (N=13,870)	Azithromycin (N=2,655)	*d*[a]	Clarithromycin (N=13,870)	Azithromycin (N=2,655)	*d*[a]
Gender						
Male	5,591 (40.31)	869 (32.73)	0.158	5,417.9 (39.06)	1,029.8 (38.79)	0.006
Female	8,279 (59.69)	1,786 (67.27)		8452.1 (60.94)	1,625.2 (61.21)	
Age, group						
Mean (± SD)	58.99 (11.58)	59.01 (12.29)	0.002	59.0 (11.65)	59.1 (12.00)	0.011
Median [IQR]	58.00 [50–68]	58.00 [49–69]		58.0 [50–68]	58.0 [50–69]	
40–49	3,383 (24.39)	712 (26.82)	0.056	3,440.4 (24.80)	656.5 (24.73)	0.002
50–59	4,203 (30.30)	740 (27.87)	0.054	4,141.0 (29.86)	785.9 (29.60)	0.006
60–69	3,304 (23.82)	575 (21.66)	0.052	3,260.1 (23.50)	605.1 (22.79)	0.017
70–79	2,410 (17.38)	503 (18.95)	0.041	2,443.7 (17.62)	496.4 (18.70)	0.028
80–99	570 (4.11)	125 (4.71)	0.029	584.8 (4.22)	111.1 (4.18)	0.002
Index period						
2011.07.01–2011.12.31	2,566 (18.50)	342 (12.88)	0.155	2,487.3 (17.93)	426.3 (16.06)	0.050
2012.01.01–2012.06.30	1,317 (9.50)	280 (10.55)	0.035	1,283.8 (9.26)	314.4 (11.84)	0.084
2012.07.01–2012.12.31	1,356 (9.78)	237 (8.93)	0.029	1,342.1 (9.68)	246.2 (9.27)	0.014
2013.01.01–2013.06.30	1,396 (10.06)	322 (12.13)	0.066	1,395.8 (10.06)	323.5 (12.18)	0.068
2013.07.01–2013.12.31	1,638 (11.81)	295 (11.11)	0.022	1,650.4 (11.90)	277.4 (10.45)	0.046
2014.01.01–2014.06.30	1,742 (12.56)	319 (12.02)	0.017	1,760.8 (12.70)	284.8 (10.73)	0.061
2014.07.01–2014.12.31	1,720 (12.40)	352 (13.26)	0.026	1,763.9 (12.72)	308.6 (11.62)	0.034
2015.01.01–2015.06.30	2,135 (15.39)	508 (19.13)	0.099	2,185.9 (15.76)	473.7 (17.84)	0.056
Comorbidities						
Chronic pulmonary disease	7,538 (54.35)	1,655 (62.34)	0.163	7,722.5 (55.68)	1,520.7 (57.28)	0.032
Hyperlipidemia	2,844 (20.50)	507 (19.10)	0.035	2,810.5 (20.26)	530.9 (20.00)	0.006
Hypertension	3,066 (22.11)	517 (19.47)	0.065	3,006.4 (21.68)	575.2 (21.66)	0.000
Diabetes without complications	1,832 (13.21)	321 (12.09)	0.034	1,806.6 (13.03)	344.3 (12.97)	0.002
Cancer	1,211 (8.73)	375 (14.12)	0.170	1,331.2 (9.60)	252.9 (9.52)	0.003
Peripheral vascular disease	804 (5.80)	112 (4.22)	0.072	767.8 (5.54)	141.6 (5.33)	0.009
Diabetes with chronic complications	510 (3.68)	78 (2.94)	0.041	493.9 (3.56)	100.1 (3.77)	0.011
Congestive heart failure	195 (1.41)	39 (1.47)	0.005	196.8 (1.42)	40.2 (1.52)	0.008
Valvular disease	33 (0.24)	12 (0.45)	0.037	37.6 (0.27)	6.8 (0.26)	0.002

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	Unadjusted data			Data adjusted by IPTW		
	Clarithromycin (N=13,870)	Azithromycin (N=2,655)	*d* [a]	Clarithromycin (N=13,870)	Azithromycin (N=2,655)	*d* [a]
Pre-existing medications						
NSAIDs (oral)	9,927 (71.57)	1,733 (65.27)	0.136	9791.2 (70.59)	1,900.4 (71.58)	0.022
Corticosteroids (oral)	5,526 (39.84)	859 (32.35)	0.156	5,360.8 (38.65)	1,043.6 (39.31)	0.014
Proton pump inhibitors (oral)	4,822 (34.77)	692 (26.06)	0.190	4,622.8 (33.33)	866.5 (32.64)	0.015
Anti-depressants (oral)	1,535 (11.07)	367 (13.82)	0.084	1,513.1 (10.91)	299.6 (11.28)	0.012
Calcium channel blocker (oral)	1,685 (12.15)	237 (8.93)	0.105	1,637.0 (11.80)	304.9 (11.48)	0.010
Angiotensin receptor blockers	1,497 (10.79)	254 (9.57)	0.041	1,468.5 (10.59)	280.2 (10.55)	0.001
Statins	1,416 (10.21)	241 (9.08)	0.038	1,390.1 (10.02)	262.7 (9.90)	0.004
Oral hypoglycemic agents	1,535 (11.07)	267 (10.06)	0.033	1,046.2 (7.54)	203.7 (7.67)	0.005
Other diuretics (oral)	1,056 (7.61)	160 (6.03)	0.063	1,019.7 (7.35)	188.6 (7.10)	0.010
Beta blocker (oral)	789 (5.69)	168 (6.33)	0.027	803.1 (5.79)	151.6 (5.71)	0.003
Corticosteroids (inhalation)	729 (5.26)	165 (6.21)	0.041	752.8 (5.43)	154.3 (5.81)	0.017
Low dose aspirin	686 (4.95)	107 (4.03)	0.044	665.3 (4.80)	131.4 (4.95)	0.007
Insulin	416 (3.00)	74 (2.79)	0.013	411.7 (2.97)	80.5 (3.03)	0.004
Loop diuretics (oral)	315 (2.27)	80 (3.01)	0.046	332.1 (2.39)	67.5 (2.54)	0.010
Antipsychotics (oral)	276 (1.99)	50 (1.88)	0.008	273.2 (1.97)	51.4 (1.94)	0.002
Other lipid lowering agents	230 (1.66)	36 (1.36)	0.025	222.5 (1.60)	41.3 (1.55)	0.004
Angiotensin converting enzyme inhibitors	156 (1.12)	27 (1.02)	0.010	153.0 (1.10)	26.9 (1.00)	0.010
Antiplatelet agents (oral)	162 (1.17)	25 (0.94)	0.022	157.4 (1.13)	33.4 (1.26)	0.012
Digoxin (oral)	35 (0.25)	10 (0.38)	0.022	37.8 (0.27)	7.6 (0.29)	0.004
Anti-coagulants (oral)	30 (0.22)	10 (0.38)	0.029	34.0 (0.24)	7.0 (0.26)	0.004

Data are reported as mean (± standard deviation), median (interquartile range), and numbers (%). [a], standardized difference of greater than >0.1 represents meaningful imbalance between the study groups. *d*, standardized difference; IPTW, inverse probability treatment weights; SD, standard deviation; IQR, interquartile range; NSAID, non-steroidal anti-inflammatory drug.

Comparison of the incidence rates of cardiovascular disease between patients with NTM disease treated with macrolide and the general population

First, we calculated the incidence rate and the 95% confidence interval (CI) of cardiovascular disease in the study subjects per 1,000 person-years assuming a Poisson distribution. Then, the standardized incidence ratio (SIR) was calculated; the observed cases were divided by the expected number of cases for each 10-year age- and gender-stratified general population in South Korea. The expected number of cases in a South Korean general population was defined as the number of subjects with cardiovascular disease in the year 2013 based on the data of the Korean National Health Insurance Service national sample cohort. This cohort comprised a representative random sample of 1,025,340 individuals, which accounts for approximately 2.2% of the entire population of South Korea (28). Byar's approximation was used to calculate the 95% CIs for SIRs (29).

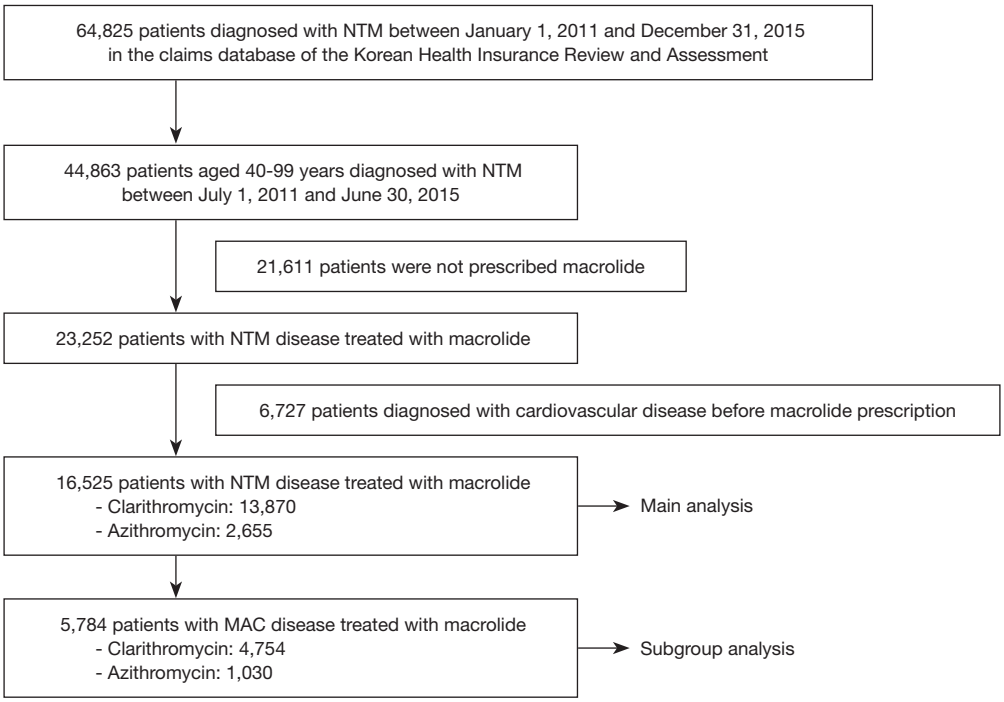

Figure 2 Study flow chart. NTM, nontuberculous mycobacteria; MAC, *Mycobacterium avium* complex.

Differences in the risk for cardiovascular disease between patients treated with clarithromycin and azithromycin

Survival curves were constructed with Kaplan-Meier estimates and compared with the use of the log-rank test. The crude hazard ratio for the association between the macrolide antibiotics and the incidence of cardiovascular disease was calculated using the Cox proportional hazard model. For more rigorous control of potential confounders, the hazard ratios were adjusted based on IPTW-weighted Cox models and were further adjusted for some important covariates that might have significant effects on the outcomes. All statistical analyses were performed using the SAS Enterprise Guide software (version 6.1, SAS Institute, Inc., Cary, NC, USA).

Results

Characteristics of the study subjects

Eligibility screening identified 16,525 patients with NTM disease who received macrolide medications (*Figure 2*). The study population had a mean (± standard deviation) age of 59.0 (±11.9). A total of 13,870 patients were prescribed clarithromycin and the remaining 2,655 were prescribed azithromycin. The baseline characteristics of the study subjects are shown in *Table 1*. Among the drugs used for the treatment of NTM, rifampin and ethambutol were the most commonly prescribed drugs with macrolide. The other concomitant medications used for NTM are presented in the *Table S3*.

Incidence of cardiovascular disease in patients with NTM disease treated with macrolide

During the study period, 277 events of cardiovascular disease were identified; these included cerebrovascular disease (n=166), cardiac arrhythmia (n=85), and acute myocardial infarction (n=32). The incidence of cardiovascular disease in patients with NTM disease treated with macrolide was 7.58 per 1,000 patients per year. As shown in *Table 2*, the SIR of cardiovascular disease in the study population was significantly higher than that in the age- and gender-stratified general population (SIR, 1.44; 95% CI, 1.27–1.61).

Table 2 The incidence of cardiovascular disease in patients with NTM disease treated with macrolide compared with the age- and gender-stratified general population

Outcome	No. of events	Sum of person-years	Incidence rate		SIR	
			Incidence rate (/1,000 person-years)	95% CI	SIR[a]	95% CI
All cardiovascular diseases						
Macrolide-treated NTM patients	277	36,553.5	7.58	6.71–8.52	1.44	1.27–1.61
General population[b]	2,714	514,087.0	5.28	5.08–5.48	1.00	
Cerebrovascular disease						
Macrolide-treated NTM patients	166	36,726.1	4.52	3.86–5.26	1.17	1.00–1.36
General population[b]	1,990	514,087.0	3.87	3.70–4.04	1.00	
Cardiac arrhythmia						
Macrolide-treated NTM patients	85	36,845.0	2.31	1.84–2.85	2.76	2.21–3.42
General population[b]	429	514,087.0	0.83	0.76–0.92	1.00	
Acute myocardial infarction						
Macrolide-treated NTM patients	32	36,934.1	0.87	0.59–1.22	1.31	0.89–1.84
General population[b]	341	514,087.0	0.66	0.59–0.74	1.00	

[a], the observed number of patients with NTM disease was divided by the expected number of cases for each 10-year age- and gender-stratified general population; [b], expected patients in the general population were defined as incident subjects with cardiovascular disease in the year 2013 using the Korean National Health Insurance Service National sample cohort. CI, confidence interval; SIR, standardized incidence ratio; NTM, nontuberculous mycobacteria.

Comparison of the risk for cardiovascular disease between patients treated with clarithromycin and azithromycin

As shown in *Figure 3*, the risk for cardiovascular disease was not different between patients treated with clarithromycin and azithromycin in the unadjusted analysis (crude hazard ratio, 0.90; 95% CI, 0.65–1.25; *Tables 3* and *4*). Further analyses adjusted by IPTW alone and IPTW with the significant covariates influencing outcome likewise revealed no difference in the cardiovascular risk between patients treated with clarithromycin and azithromycin (adjusted hazard ratio, 0.91 and 0.90; 95% CI, 0.66–1.26 and 0.65–1.24, respectively; *Table 4*).

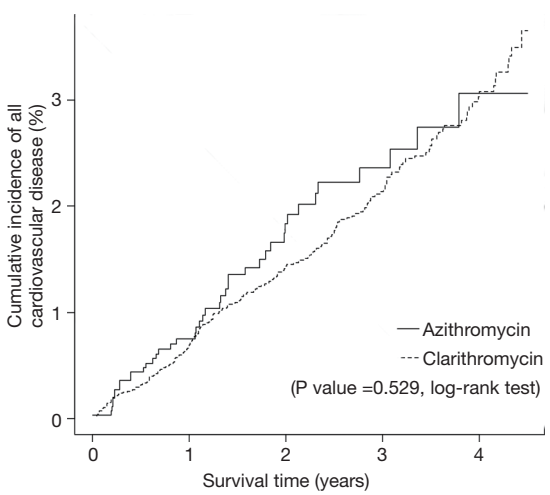

Figure 3 Kaplan-Meier estimates of the cardiovascular disease development in patients with nontuberculous mycobacterial disease according to the macrolide used.

Subgroup analysis of the risk for cardiovascular disease in patients with MAC disease treated with macrolide

As shown in *Figure 2*, 5,784 patients were identified as having MAC disease. Subgroup analysis of these patients showed generally similar results, but SIR for cardiovascular disease was higher than that of NTM disease compared with general population (SIR, 1.96; 95% CI, 1.65–2.30) (*Table S4*). In addition, we found no difference in the risks for cardiovascular disease between patients with MAC disease treated with clarithromycin and those treated with

Table 3 Comparison of the incidence of cardiovascular disease in patients with nontuberculous mycobacterial disease according to the macrolide used

Outcome	No. of events	Sum of person-years	Incidence rate (/1,000 person-years)	95% CI
All cardiovascular diseases				
Clarithromycin	235	31,446.6	7.47	6.55–8.49
Azithromycin	42	5,106.9	8.22	5.93–11.12
Cerebrovascular disease				
Clarithromycin	140	31,599.3	4.43	3.73–5.23
Azithromycin	26	5,126.8	5.07	3.31–7.43
Cardiac arrhythmia				
Clarithromycin	74	31,691.2	2.34	1.83–2.93
Azithromycin	11	5,153.8	2.13	1.07–3.82
Acute myocardial infarction				
Clarithromycin	27	31,771.8	0.85	0.56–1.24
Azithromycin	5	5,162.2	0.97	0.31–2.26

CI, confidence interval.

Table 4 Comparison of the risk for cardiovascular disease between patients treated with clarithromycin and azithromycin

Outcome	Unadjusted analysis		Adjusted analysis by IPTW		Adjusted analysis by IPTW and covariates	
	Crude HR	95% CI	HR adjusted by IPTW	95% CI	HR adjusted by IPTW and covariates[a]	95% CI
All cardiovascular diseases						
Clarithromycin	0.90	0.65–1.25	0.91	0.66–1.26	0.90	0.65–1.24
Azithromycin	1.00		1.00		1.00	
Cerebrovascular disease						
Clarithromycin	0.86	0.57–1.31	0.86	0.57–1.30	0.86	0.57–1.29
Azithromycin	1.00		1.00		1.00	
Cardiac arrhythmia						
Clarithromycin	1.09	0.58–2.05	0.99	0.54–1.82	0.99	0.54–1.82
Azithromycin	1.00		1.00		1.00	
Acute myocardial infarction						
Clarithromycin	0.87	0.33–2.26	1.21	0.41–3.60	1.19	0.40–3.53
Azithromycin	1.00		1.00		1.00	

[a], adjusted for IPTW and the significant covariates, including age, gender, and concomitant medication (corticosteroids, proton pump inhibitors, and non-steroidal anti-inflammatory drugs) that influenced outcomes. HR, hazard ratio; CI, confidence interval; IPTW, inverse probability treatment weights.

azithromycin (*Table S5*), although this interpretation may be biased because of the small number of cardiovascular events in this subgroup of patients.

Discussion

NTM disease can lead to various complications, such as substantial decline in lung function (30), respiratory failure (31), and mortality (32). However, the level of risk for cardiovascular disease in patients with NTM disease treated with macrolide is unknown. To the best of our knowledge, this was the first study that aimed to assess this issue. Based on our analyses, the most important finding was the significantly higher risk for cardiovascular disease in NTM patients aged 40 years or older treated with macrolide than in the age- and gender-stratified general population. This finding was more evident in patients with MAC disease. Further, the increased risk for developing cardiovascular disease was not different between patients treated with clarithromycin and azithromycin.

There are several plausible explanations for the increased incidence of cardiovascular disease in patients with NTM disease treated with macrolide. First, the inability to eradicate NTM from the lungs can lead to an exuberant inflammatory response that is modulated by the immune and airway epithelial cells through the release of inflammatory cytokines (33). This condition can result in endothelial dysfunction and the exposure/release of factor VII, tissue factor, von Willebrand factor, and subendothelial collagen, creating a pro-coagulant state (6) that can lead to acute cardiovascular events. Second, the increased cardiovascular risk may be associated with bronchiectasis which is frequently found in patients with NTM lung disease (24). Bronchiectasis is known as a predisposing factor for NTM infection; conversely, NTM infection can lead to development of bronchiectasis (33). Of note, patients with bronchiectasis have an increased cardiovascular risk, possibly due to systemic inflammation, that may contribute to the development of atherosclerosis (34). Considering that the most common form of NTM lung disease is a nodular bronchiectatic type (35) and given the close association between bronchiectasis and NTM lung disease, bronchiectasis may be a link between NTM lung disease and acute cardiovascular events. Third, macrolides accumulate and promote the growth of macrophages, which results in plaque formation due to thrombosis (10,36). Fourth, because of the potassium channel blocking properties, macrolides are known to prolong the QT interval and increase the risk for arrhythmias (13,37). Arrhythmia may also play a role in plaque rupture that leads to cardiovascular events (11). However, given the lack of experimental evidence to support specific mechanisms behind the association between macrolide antibiotics and cardiovascular risk in NTM lung disease, future studies are needed to elucidate the mechanisms explaining this finding.

A number of studies that compared the cardiovascular disease risk between clarithromycin and azithromycin showed conflicting results. For example, a study by Chou *et al.* in Taiwan reported that azithromycin was associated with a significant increase in the risks for ventricular arrhythmia and cardiovascular death compared with amoxicillin–clavulanate; in contrast, clarithromycin and ciprofloxacin were not associated with adverse cardiac outcomes (14). In animal studies, clarithromycin was demonstrated to have more prominent proarrhythmic potential than azithromycin (15,16). Meanwhile, one study in Canada showed no significant differences between patients treated with clarithromycin and azithromycin in terms of 12 composite outcomes, including acute myocardial infarction, arrhythmia, and ischemic stroke (17). In the present study, no difference in the risk for cardiovascular disease was found between patients treated with clarithromycin and azithromycin.

The use of macrolide has been demonstrated beneficial in several respiratory diseases due to its anti-inflammatory effect (38-40). However, we found a higher cardiovascular risk in patients treated with macrolides than in the general population. Two lines of reasoning could explain this result. First, the impact of macrolides on the cardiovascular risk may have been stronger than the anti-inflammatory effects in patients with NTM lung disease. Second, NTM lung disease itself may have led to a significantly higher incidence of cardiovascular disease despite the macrolide anti-inflammatory effects, resulting in a higher risk in patients with NTM lung disease than that in the general population. Although at the moment it is impossible to understand how or why the anti-inflammatory effects of macrolides were diminished in the present study, our result is still useful to physicians because the increased acute cardiovascular events risk among this population suggests that close patient monitoring and proper preventive strategies may be necessary.

We assumed that the effects of the macrolide were prolonged even after discontinuing the drug, but one study suggested that cardiovascular disease immediately developed within a few days after drug intake and did not persist after

the course of therapy ended (13). The design of the present study did not allow precise assessment of this short-term effect of macrolides on cardiovascular disease. Accordingly, we performed a subgroup analysis for patients with MAC disease with the assumption that the effects of macrolide disappeared soon after discontinuing the drug, but within a designated grace period (additional methods is provided in the Supplementary Data). The results of this analysis were generally the same as the results of the analysis of the overall study population (see *Tables S6*,*S7*).

Our current study had several limitations. Most importantly, the diagnoses of NTM disease and the prescription of macrolide were solely dependent on the HIRA claims data, which were less accurate than the diagnoses made according to standardized criteria. Second, use of the HIRA data did not enable us to exclude patients with NTM disease other than lung infections, such as lymphadenopathy and skin and soft tissue infections. Third, although one of the important results of our study was the more pronounced risk for cardiovascular disease in MAC disease than in NTM disease, the definition of MAC disease may not have been accurate. That is, our definition of MAC disease based on a combination of rifampin and ethambutol with macrolide can also be used in the other common NTM species, such as *Mycobacterium kansasii* (41). However, *M. kansasii* has been shown to represent only 1–2% of all NTM isolates and pathogens in NTM lung disease in South Korea (41). Fourth, we failed to include the body mass index and the lifestyle factors, such as alcohol consumption, smoking, and physical activity, which are known to influence the risk for cardiovascular disease. Lastly, in this study based on HIRA data, we could not tell whether the increased cardiovascular risk was due to the NTM disease itself, to the macrolides, or to both. We had to exclude patients identified with ICD-10 codes for NTM without macrolide treatment, because it was unclear whether they actually met the ATS/IDSA NTM lung disease diagnostic criteria. We only included data from patients with macrolide prescriptions. However, it should be noted as a limitation that the macrolides may have been used to treat conditions other than NTM disease (e.g., pneumonia).

In conclusion, the incidence of cardiovascular disease was significantly higher in patients aged 40 years or older treated with macrolide for nontuberculous mycobacterial disease than in the general population. This risk was not different between patients treated with clarithromycin and azithromycin.

Acknowledgements

We thank the Korean Health Insurance Review and Assessment Service and the National Health Insurance Service for providing the insurance claims data.
Funding: This research was supported by the Asan Institute for Life Sciences, Asan Medical Center, Seoul, Korea (grant number: 2016–617).

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: This study protocol was approved by the Institutional Review Board of Asan Medical Center, Seoul, South Korea (IRB No. 2016-0880). Informed consent was waived because the study used an existing database that was provided in a de-identified format.

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Cite this article as: Kang J, Kim YJ, Shim TS, Jo KW. Risk for cardiovascular disease in patients with nontuberculous mycobacteria treated with macrolide. J Thorac Dis 2018;10(10):5784-5795. doi: 10.21037/jtd.2018.09.145

Supplementary

Table S1 Baseline comorbidity definitions and diagnosis codes

No.	Disease	ICD-10 code (KCD-6 code)
1	Diabetes without complications	E10, E11, E12, E13, E14, E10.0, E10.1, E10.6, E10.8–E11.1, E11.6, E11.8–E12.1, E12.6, E12.8–E13.1, E13.6, E13.8–E14.1, E14.6, E14.8, E14.9
2	Diabetes with chronic complications	E10.2–E10.5, E10.7, E11.2–E11.5, E11.7, E12.2–E12.5, E12.7, E13.2–E13.5, E13.7, E14.2–E14.5, E14.7
3	Hyperlipidemia	E78.0–78.5
4	Hypertension	I10.x, I11.x–I13.x, I15.x
5	Congestive heart failure	I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5–I42.9, I43.x, I50.x
6	Arrhythmia	I44.1–I44.3, I45.6, I45.9, I47.x–I49.x, R00.0, R00.1, R00.8, T82.1, Z45.0, Z95.0
7	Valvular disease	A52.0, I05.x–I08.x, I09.1, I09.8, I34.x–I39.x, Q23.0–Q23.3, Z95.2–Z95.4
8	Peripheral vascular disease	I70.x, I71.x, I73.1, I73.8, I73.9, I77.1, I79.0, I79.2, K55.1. K55.8, K55.9, Z95.8, Z95.9
9	Chronic pulmonary disease	I27.8, I27.9, J40.1–J40.9, J41.x–J47.x, J60.x–J67.x, J68.4, J70.1, J70.3
10	Moderate to severe liver disease	I85.0, I85.9, I86.4, I98.2, K70.4, K71.1, K72.1, K72.9, K76.5, K76.6, K76.7
11	Renal disease	I12.0, I13.1, N03.2-N03.7, N05.2–N05.7, N18.x, N19.x, N25.0, Z49.0–Z49.2, Z94.0, Z99.2
12	Cancer	C00.x–C97.x
13	Rheumatologic disease	M05.x, M06.x, M31.5, M32.x–M34.x, M35.1, M35.3, M36.0
14	Gout	M10.x, M140

ICD-10, International Classification of Disease and Related Health Problems, tenth revision; KCD-6, Korean Classification of Disease, sixth edition.

Table S2 Types of pre-existing medication

No.	Class	Medication
1	Angiotensin receptor blockers	Losartan, eprosartan, valsartan, irbesartan, candesartan, telmisartan, olmesartan, fimasartan
2	Angiotensin converting enzyme inhibitors	Captopril, enalapril maleate, lisinopril, perindopril tertbutylamine, ramipril, cilazapril, fosinopril, moexipril, temocapril, imidapril, alacepril
3	Beta blockers (oral)	Propranolol, sotalol, metoprolol, atenolol, betaxolol, bevantolol, bisoprolol, celiprolol, s-atenolol, nebivolol, carvedilol, amosulalol
4	Calcium channel blockers (oral)	Amlodipine, felodipine, isradipine, nicardipine, nifedipine, nisoldipine, nitrendipine, lacidipine, manidipine, barnidipine, lercanidipine, cilnidipine, benidipine, efonidipine, verapamil, diltiazem
5	Low-dose aspirin	Low dose aspirin
6	Anticoagulants	Warfarin
7	Antiplatelet agents	Clopidogrel, ticlopidine, triflusal, prasugrel, cilostazol, dabigatran etexilate, rivaroxaban
8	Digoxin (oral)	Digoxin
9	Loop diuretics (oral)	Furosemide, torasemide
10	Other diuretics (oral)	Hydrochlorothiazide, spironolactone, amiloride, tolvaptan
11	Statins	Simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin, pitavastatin
12	Other lipid lowering agents	Bezafibrate, gemfibrozil, fenofibrate, colestyramine, nicotinic acid, acipimox, omega-3-triglycerides incl. Other esters and acids, ezetimibe
13	Oral hypoglycemic agents	Metformin, glibenclamide, glipizide, gliclazide, glimepiride, acarbose, voglibose, pioglitazone, lobeglitazone, sitagliptin , vildagliptin, saxagliptin, alogliptin, linagliptin, gemigliptin, repaglinide, nateglinide, mitiglinide
14	Insulin	Human insulin, insulin glulisine, insulin lispro, insulin aspart, insulin glargine, insulin determine
15	Antidepressants	Imipramine, clomipramine, amitriptyline, nortriptyline, dosulepin/dothiepin, amoxapine, quinupramine, fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, escitalopram, moclobemide, trazodone, mirtazapine, bupropion, tianeptine, venlafaxine, milnacipran, duloxetine, hyperici herba
16	Antipsychotics (oral)	Chlorpromazine, levomepromazine, perphenazine, haloperidol, bromperidol, clozapine, olanzapine, quetiapine, sulpiride, amisulpride, lithium, risperidone, zotepine, aripiprazole
17	Corticosteroids (oral)	Fludrocortisone, betamethasone, dexamethasone, methylprednisolone, prednisolone, triamcinolone, hydrocortisone, deflazacort, beclomethasone
18	Corticosteroids (inhalation)	Triamcinolone, budesonide, beclomethasone
19	NSAIDs (oral)	Pyrazinobutazone, sulindac, diclofenac, etodolac, lonazolac, acemetacin, proglumetacin, ketorolac, aceclofenac, piroxicam, lornoxicam, meloxicam, ibuprofen, naproxen, fenoprofen, tiaprofenic acid, oxaprozin, dexibuprofen, loxoprofen, pranoprofen, zaltoprofen, mefenamate, flufenamate, celecoxib, nabumetone, nimesulide, diacerhein, talniflumate, clonixin lysinate, salsalate, morniflumate, emorfazone, imidazole salicylate
20	Proton pump inhibitors (oral)	Omeprazole, pantoprazole, s-pantoprazole, lansoprazole, rabeprazole, esomeprazole, dexlansoprazole, ilaprazole

NSAID, non-steroidal anti-inflammatory drug.

Table S3 Concomitantly used medications with macrolides for nontuberculous mycobacteria

Medication	Clarithromycin (N=13,870)	Azithromycin (N=2,655)	P value*
Rifampicin	5,064 (36.51)	1,061 (39.96)	0.001
Ethambutol	4,949 (35.68)	1,076 (40.53)	<0.0001
Rifampicin and ethambutol	4,754 (34.28)	1,030 (38.79)	<0.0001
Moxifloxacin	1,051 (7.58)	232 (8.74)	0.041
Amikacin	915 (6.60)	233 (8.78)	<0.0001
Isoniazid	897 (6.47)	108 (4.07)	<0.0001
Streptomycin	612 (4.41)	163 (6.14)	<0.0001
Imipenem or cefoxitin	480 (3.46)	178 (6.70)	<0.0001
Cefoxitin	282 (2.03)	145 (5.46)	<0.0001
Imipenem	272(1.96)	78 (2.94)	<0.0001

*, P value was estimated by chi-square test.

Table S4 Incidence of cardiovascular disease in patients with MAC disease treated with macrolide compared with the age- and gender-stratified general population

Outcome	No. of events	Sum of person-years	Incidence rate		SIR	
			Incidence rate (/1,000 person-years)	95% CI	SIR*	95% CI
All cardiovascular diseases						
Macrolide-treated MAC patients	147	14,229.1	10.33	8.73–12.14	1.96	1.65–2.30
General population#	2714	514,087.0	5.28	5.08–5.48	1.00	
Cerebrovascular disease						
Macrolide-treated MAC patients	87	14,325.4	6.07	4.86–7.49	1.57	1.26–1.94
General population#	1,990	514,087.0	3.87	3.70-4.04	1.00	
Cardiac arrhythmia						
Macrolide-treated MAC patients	48	14,383.8	3.34	2.46–4.42	4.00	2.95–5.30
General population#	429	514,087.0	0.83	0.76–0.92	1.00	
Acute myocardial infarction						
Macrolide-treated MAC patients	14	14,438.7	0.97	0.53–1.63	1.46	0.80–2.45
General population#	341	51,4087.0	0.66	0.59–0.74	1.00	

*, the observed cases of nontuberculous mycobacterial patients were divided by the expected cases for each 10-year age group- and gender-stratified general population; #, expected cases in the general population were defined as incident subjects with cardiovascular disease in the year of 2013 using the Korean National Health Insurance Service-National sample cohort. CI, confidence interval; SIR, standardized incidence ratio; MAC, *Mycobacterium avium* complex.

Table S5 Risk for cardiovascular disease according to the macrolide used in patients with *Mycobacterium avium* complex disease

Outcome	Unadjusted analysis		Adjusted analysis by IPTW		Adjusted analysis by IPTW and covariates	
	Crude HR	95% CI	HR adjusted by IPTW	95% CI	HR adjusted by IPTW and covariates*	95% CI
All cardiovascular diseases						
Clarithromycin	0.82	0.54–1.26	0.86	0.57–1.31	0.89	0.58–1.34
Azithromycin	1.00		1.00		1.00	
Cerebrovascular disease						
Clarithromycin	0.84	0.48–1.46	0.92	0.52–1.60	0.94	0.54–1.64
Azithromycin	1.00		1.00		1.00	
Cardiac arrhythmia						
Clarithromycin	0.89	0.42–1.91	0.91	0.43–1.93	0.94	0.45–1.99
Azithromycin	1.00		1.00		1.00	
Acute myocardial infarction						
Clarithromycin	0.63	0.18–2.28	0.60	0.18–2.00	0.60	0.18–2.02
Azithromycin	1.00		1.00		1.00	

*, adjusted for IPTW and the significant covariates, including age, gender, and concomitant medications (corticosteroids, proton pump inhibitors, and non-steroidal anti-inflammatory drugs) that influenced outcomes. HR, hazard ratio; CI, confidence interval; IPTW, inverse probability treatment weights.

Additional methods

Because previous study have shown that the cardiovascular side effects of macrolides developed within several days of administration, we set a grace period based on the assumption that the effects of the macrolides would resolve soon after discontinuation of the drug. We calculated the duration from initiation to discontinuation of macrolide use based on the number of days between refills. In cases in which the macrolide was prescribed for less than 30 days, we allowed a 30-day maximum permissible refill gap of the prescription between the end of the latest prescription and the date of the subsequent dose. In cases in which the macrolide was prescribed for more than 30 days, twice the prescribed period plus 30 days was the designated permissible refill gap. The other methods, definition of other exposure assessments, occurrence of outcome, and switch to another macrolide were the same as those of the original analysis.

Table S6 Incidence of cardiovascular disease in patients with MAC disease treated with macrolide compared with the age- and gender-stratified general population, based on the assumption of the short-term effect of macrolides on cardiovascular disease after discontinuation

Outcome	No. of event	Sum of person-years	Incidence rate		SIR	
			Incidence rate (/1,000 person-years)	95% CI	SIR*	95% CI
All cardiovascular diseases						
Macrolide-treated MAC patients	47	5,225.8	8.99	6.61–11.96	1.70	1.25–2.27
General population#	2,714	514,087.0	5.28	5.08–5.48	1.00	
Cerebrovascular disease						
Macrolide-treated MAC patients	28	5,235.5	5.35	3.55–7.73	1.38	0.92–2.00
General population#	1,990	514,087.0	3.87	3.70-4.04	1.00	
Cardiac arrhythmia						
Macrolide-treated MAC patients	15	5,245.2	2.86	1.60–4.72	3.43	1.92–5.65
General population#	429	514,087.0	0.83	0.76–0.92	1.00	
Acute myocardial infarction						
Macrolide-treated MAC patients	4	5,252.5	0.76	0.21–1.95	1.15	0.31–2.94
General population#	341	51,4087.0	0.66	0.59–0.74	1.00	

*, the observed cases of nontuberculous mycobacterial patients were divided by the expected cases for each 10-year age group- and gender-stratified general population; #, expected cases in general population were defined as incident subjects with cardiovascular disease in the year of 2013 using the Korean National Health Insurance Service-National sample cohort. CI, confidence interval; SIR, standardized incidence ratio; MAC, *Mycobacterium avium* complex.

Table S7 Risk for cardiovascular disease according to the macrolide used in patients with *Mycobacterium avium* complex disease, based on the assumption of the short-term effect of macrolides on cardiovascular disease after discontinuation

Outcome	Unadjusted analysis		Adjusted analysis by IPTW		Adjusted analysis by IPTW and covariates	
	Crude HR	95% CI	HR adjusted by IPTW	95% CI	HR adjusted by IPTW and covariates*	95% CI
All cardiovascular diseases						
Clarithromycin	0.85	0.43–1.72	1.03	0.48–2.20	1.05	0.49–2.25
Azithromycin	1.00		1.00		1.00	
Cerebrovascular disease						
Clarithromycin	0.67	0.29–1.58	0.76	0.31–1.89	0.79	0.32–1.97
Azithromycin	1.00		1.00		1.00	
Cardiac arrhythmia						
Clarithromycin	0.93	0.26–3.32	1.29	0.29–5.70	1.38	0.31–6.12
Azithromycin	1.00		1.00		1.00	
Acute myocardial infarction						
Clarithromycin	–	–	–	–	–	–
Azithromycin	1.00		1.00		1.00	

*, adjusted for IPTW and the significant covariates, including age, gender, and concomitant medications (corticosteroids, proton pump inhibitors, and non-steroidal anti-inflammatory drugs) that influenced outcomes. HR, hazard ratio; CI, confidence interval; IPTW, inverse probability treatment weights.