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The association between Tendon Ruptures and Use of Fluoroquinolone, and other oral antibiotics in 1.1 million U.S. senior Medicare beneficiaries

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Abstract (Max 300 words, 294 now)

Objectives: To assess the association of fluoroquinolone use with tendon ruptures compared to no fluoroquinolone and that of the four most commonly prescribed non-fluoroquinolone antibiotics in the US.

Design: Prospective observational study.

Setting: U.S. senior enrolled in the federal old-age, survivors insurance program.

Participants: 1,186,013 Medicare fee-for-service beneficiaries and their inpatient, outpatient, prescription drug records were used.

Interventions: Seven oral antibiotics, fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin) and amoxicillin, amoxicillin-clavulanate, azithromycin and cephalexin.

Primary and Secondary Outcome measures: All tendon ruptures combined, and three types of tendon ruptures by anatomic site, Achilles tendon rupture, rupture of rotator cuff and tendon ruptures on other anatomic sites.

Results: Of three fluoroquinolones, only levofloxacin exhibited a significant increased risk of tendon ruptures - 16%, and 112% for rotator cuff and Achilles tendon rupture respectively in the ≤30 day window. Ciprofloxacin and moxifloxacin exhibited little to no increased risk of tendon ruptures. Notably, the risk of levofloxacin never exceeded the risk of the non-fluoroquinolone, cephalexin in any comparison.

Among the non-fluoroquinolone antibiotics, amoxicillin, amoxicillin-clavulanate, and azithromycin exhibited none to benign risk of tendon rupture. Cephalexin exhibited modest to large *increased* risk of tendon rupture at ≤30 day window across all sites and its risk exceeded the risk for levofloxacin.

Conclusions: In our study, fluoroquinolones as a class were not associated with the increased risk of tendon ruptures. Neither ciprofloxacin nor moxifloxacin exhibited any risk for tendon ruptures. Levofloxacin did exhibit significant increased risk. Cephalexin with no reported effect on metalloprotease activity had an equal or greater risk than levofloxacin; so we question whether metalloprotease activity has any relevance to observed associations with tendon rupture. Confounding by indication bias may be more relevant and should be given more consideration as explanation for significant associations in observational studies of tendon rupture.

Strengths and limitations of this study

- We conducted a large (more than 1 million US senior subjects) prospective study of outpatient prescription drug records to assess the association between the use of fluoroquinolones and the occurrence of tendon ruptures compared to the most commonly used non-fluoroquinolone oral antibiotics.
- Our study included all oral fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin) prescribed in the US and the four most commonly prescribed non-fluoroquinolone antibiotics: amoxicillin, amoxicillin-clavulanate, azithromycin and cephalexin as controls.
- In addition to reporting the risk of any tendon rupture, we also reported the risk of three types of tendon ruptures by anatomic site 1) Achilles tendon rupture, 2) rupture of rotator cuff and 3) tendon ruptures on other anatomic sites as separate outcomes.
- This study is possibly only applicable to U.S. senior, aged 65 or more, Medicare fee-for-service beneficiaries.
- We had no options to verify claims diagnoses via chart review.

Introduction

Fluoroquinolones (FQ) are among the most widely prescribed antibiotics in the outpatient setting[1,2] due to their broad spectrum treatment of bacteria found in respiratory, urinary, joint, and skin infections. Several observational studies have reported the association between the use of FQs and tendinitis and tendon rupture (TR), especially of the Achilles tendon[3–12] and the FDA issued black box warnings to FQ antibiotics beginning in 2008.[13] The warning was updated in 2016 to recommend using alternative antibiotics when possible.[14,15] The fact that FQs upregulate the production of metalloproteinase (MMP) enzymes with collagenase activity that could weaken tendons is taken as a mechanism to explain this reported risk.[16–18]

Studies that reported association between FQ use and TR used one or more other antibiotics as controls. One study compared the FQ rupture rates with patients using azithromycin, the most frequently used oral antibiotic in the US. Only two focused principally on TR risk among the elderly. None compared TR rates of *FQs* with those of cephalexin -- the 3rd most commonly prescribed oral antibiotic in the US.

The Virtual Research Data Center (VRDC) of Center for Medicare and Medicaid Services (CMS)[19] carries more than 10 years of Medicare claims, which include information about the usage of prescription drugs and encounter diagnoses (including tendon ruptures). It also carries information about 42 major chronic diseases, demographic characteristic and vital status. We conducted a large observational study using the VRDC to assess the association of FQ antibiotics with TR compared to that of

the four most commonly prescribed non-FQ antibiotics in the US. Here we report the results of that analysis.

Methods

Patient and public involvement

Patients or the public were not involved in the design of the study.

Study population

We derived our study population from a 20% random sample of Medicare prescription drug coverage (Part D) fee-for-service enrollees who first enrolled in the Medicare under old age and survivors insurance within a month of age 65 (779-781 month-old) and on or after 1/1/2007 - the first full year of Part D prescriptions availability. We included claim data through 12/31/2016, the end of VRDC claim data available to us. All of the VRDC data is de-identified and researchers must perform all of their analysis within the VRDC computer systems, and can only pull statistical results from it.[19] We obtained approvals for these studies from the CMS privacy board and NIH OHSRP as not human subject studies.

We required subjects to be continuously enrolled in hospital insurance (Part A) and medical insurance (Part B) to assure we had full outpatient and inpatient claims data, which are not available for nearly 20% of patients with Part D only.[20] To obtain an incident cohort of TR patients, we excluded (washed out) individuals with TRs recorded

in the first year of their Medicare entitlement.[21] In order to assure sufficient follow-up, we excluded patients with less than 1-year follow-up (See Figure 1 Consort Diagram).

Primary Outcome

We identified patients with TR based upon International Classification of Diseases (ICD)-9-CM codes of 726.13, 727.60-727.69, and ICD-10-CM codes of M66.2, M66.3, M66.8, M66.9, and M75.1. We combined all TRs and reported them as one outcome, and report three types of TRs by anatomic site 1) Achilles tendon rupture, 2) rupture of rotator cuff and 3) TRs on other anatomic sites as separate outcomes. We focused on Achilles TR because it was the sole focus of many prior studies and on rotator cuff TR because it is the predominant TR of the elderly. We lumped the remaining as "other TRs".

Study antibiotics

As a study antibiotic, we included all three oral FQs prescribed in the US -- moxifloxacin (MXF), ciprofloxacin (CIP), levofloxacin (LVX), which is the active stereoisomer of ofloxacin. As controls, we also included the four most frequently prescribed non-FQ oral antibiotics - amoxicillin (AMX), amoxicillin clavulanate (AMC), azithromycin (AZT) and cephalexin (LEX). Five of our study antibiotics, AZT, AMX, AMC, CIP and LEX, were the top five U.S. antibiotic agents in 2011.

Statistical Analysis

We analyzed each of the four TR outcomes in separate Fine-Gray competing risk regression analyses with death as the competing risk.[22,23] Patients became eligible for "the study" at their Medicare enrollment but prescription data did not become available until their Part D enrollment. We followed them from their entry in Part D (while accounting for left truncation[24]) until their death, switch to a capitated plan, disenrollment from Medicare or 12/31/2016 – whichever came first. We adjusted hazard ratio (HR) of each study antibiotic for concurrent use of other study antibiotics and adjusted for calendar year of subject's Part D entry, to account for secular trends. We also adjusted each HR for patient's characteristics, income, gender, race, rural residency (Yes/No) and also for 42 chronic conditions from the Medicare Master Beneficiary Summary File (MBSF)[25] with >1% prevalence, as a measure of overall health. Based upon monthly indicators of dual-eligibility and Low Income Subsidy (LIS) status, we separated study individuals into three groups: 1) dual whose income is <135% Federal Poverty Line (FPL); 2) non-dual LIS whose income is between 135 and 150% FPL; and non-dual no LIS whose income is >150% FPL. We used this variable in the analysis as a surrogate for economic status.[26]

We assumed that patients were on a given kind of study drug from the prescription dispensing date to the end of days of supply. We did not distinguish between different brands of a study drugs. Following the approach of prior studies,[3–5] we separated subjects by temporal exposure within each study drug, including groups for never exposed, exposed within 30 days, 31-60 days, and >60 days. Thus, by this approach we could detect the presumed short term action of the FQ's on tendons and avoid the risk of

non-differential misclassification that can occur with too simple (yes/no) drug exposure measures.[27] In order to minimize the immortal time bias, we treated all drug usage measures and all patients characteristics, except gender and race, as time-varying covariates.[28,29] In order to mitigate selection bias toward use of any study antibiotics, we employed a propensity score (PS) approach.[30,31] We first derived a PS of taking any of study antibiotics as a function of patient's characteristics at the date of the first antibiotic use after Part D entry from a multiple logistic regression. We used the median days to the first study antibiotic use in patients taking study antibiotics as the cutoff time for subjects taking no study antibiotics. We performed our analyses with an inverse propensity score weight (IPSW) excluding individuals with the PS below 0.1 and above 0.9, to mitigate poorer performance in the presence of a strong treatment-selection process.[32] In post-hoc analyses, we also compared the risk of TR of each study antibiotics to that of every other study antibiotic on a pairwise basis.

Results

Study population and Secular trend

From our 20% sample of Part D enrollees, 1,186,013 patients satisfied all our selection criteria including the washout of individuals with TR in their first year of Medicare (Figure 1 Consort Diagram). Follow-up began with an individual's enrollment in Part D program (median (IQR) 0 (0-122) days from the Medicare entitlement). We followed them for a median of 3.7 years (total 4,736,653 patient-years) until the their first diagnosis of TR (3.7%), death (5.0%), switch from fee-for-service to health maintenance organization (HMO) plans (12.5%), disenrollment from Medicare (<1%) or study end on

12/31/2016 (78.8%), whichever came first. Patients had their first post enrollment claim with a diagnosis of TR at a median age of 68.5 (IQR 67.2-70.4). The proportions of non-Hispanic White, female and rural residents were 81.2%, 57.9%, and 22.7% respectively. About a fifth of patients received federal/state subsidies, i.e. Medicaid coverage on top of Medicare (dual 16.1%) or assistance in paying their Part D premium and coinsurance/copayment (non-dual LIS 2.6%). Among the 42 Medicare chronic disease covariates, hypertension (68.5%), hyperlipidemia (69.5%), cataract (47.2%), rheumatoid arthritis/osteoarthritis (38.6%), anemia (32.0%), ischemic heart disease (27.5%), and chronic kidney disease (18.7%) were the seven most prevalent (Table 1).

Of the 438,387 (37.0%) study patients who took a FQ prescription, 71.8%, 49.5% and 5.3% ever took CIP, LVX and MXF respectively. Of 737,446 (62.2%) of patients who took a non-FQ antibiotic, the figures were 55.9%, 46.2%, 35.2% and 33.0% for AZM, AMX, LEX, and AMC, respectively. Patients who took one or more study antibiotics took a median (IQR) of 3.0 (1.0-6.0) study antibiotic prescriptions and took a median (IQR) 2.0 (1.0-3.0) different study antibiotics during the observation period.

Secular trends in study antibiotics usage existed. MXF usage declined precipitously from 5.0% in 2007 to almost zero in 2016 – overweighting the MXF statistics for early entrants into Medicare and yielding a longer mean follow up time. CIP use hit a peak, and LVX, a nadir, in 2011. The use of AMX, AMC and LEX trended slowly upward (Supplementary Figure 1). The mode (median) of supply durations for each antibiotics were 10 (7) for AMX, 10 (10) for AMC, 5 (5) for AZM, 10 (7) for LEX, 7 (7) for CIP, 10 (7) for LVX,

10 (11) for MXF. About thirty percent of patients were never exposed to any one of the study antibiotics during the study period.

Unadjusted figures for TR prevalence across each of the seven study antibiotic users and the no study antibiotic users ranged from a high of 5.6% for MXF to a low of 3.0% for no antibiotic (Table 1). Except for MXF, the *unadjusted* prevalence of TRs associated with each non-FQ antibiotic was *greater than* or equal to that of each FQ antibiotic. The TR rates per 1000 patient-years followed the same pattern, with the non-FQ antibiotics topping the rates of all FQs except MXF (which had the highest rate), possibly due to overweighting of MXF usage in the early years of the study. The study subjects who ever took an FQ had the highest unadjusted rate of death per 1000 person-years. LVX's death rate was nearly twice the rate of each non-FQ antibiotics. The size of the associations with diseases like diabetes, chronic renal failure and heart failure paralleled the magnitude of the death rates and was generally higher with FQs than non-FQ antibiotics (Table 1).

Primary Analysis

Table 2 presents HRs for all covariates in our Fine-Gray competing risk regression with IPSW, for all tendon ruptures taken together. Being a female (vs. male), African-American, Hispanic, and Asian (vs. white), being Dual or non-Dual LIS (vs. non-Dual no LIS) and living in a rural area were all associated with a *reduced* risk of tendon rupture. These risk reductions were 24% or more for all but Hispanics and rural residency

covariates, and the reductions were similar across all anatomic sites. In general, life threatening chronic disease, such as COPD, heart failure and colorectal/lung/endometrial cancers were associated with a lower risk of TR in a range of 15-60% below control possibly due to constrained physical activity and/or shortened life span. Notably, diabetes and chronic renal disease, previously reported as risk factors for TR,[33,34] exhibited no increased TR risk. Mobility impairments had reduced risk of TR similar to that of the severe life threatening diseases, likely due to reduced activity. Most diseases with low life threats such as cataract, glaucoma, depression, asthma, hyperlipidemia, hypertension, prostatic hyperplasia, migraine/other chronic headache, and deafness/hearing impairment exhibited risks of 10 to 40% *above* controls probably for reasons related to longer life spans and less inhibited activity. Ischemic heart did not fit the mold of sicker equals lower TR risk. Patients with rheumatoid arthritis/osteoarthritis were a special case and had TR risk of 183% *above* control possibly due to joint and associated tendon inflammation with these disorders. Fibromyalgia/chronic pain and fatigue also exhibited a 40% increased risk of TR possibly also due to an inflammatory component.

The Achilles tendon carries the full force of the extra weight carried by obese patients and obesity was associated with a significant (21%) increase in Achilles TR ruptures while its effect on other TR classes was significant but miniscule (4-6%) (Data not shown).

Effect of antibiotics

Table 3 shows the risk associated with each study antibiotic broken down by time lag between the antibiotic use and the claim reported TR, as well as by anatomic sites. Of the

total 44,098 patients with any TR occurrence, complete rupture of rotator cuff represented the major share (80.7%), followed by other TRs (16.8%) and Achilles TR (2.5%). In the survival analysis we followed patients until the first occurrence of TR; so, these figures count only the first TR occurrence independent of anatomic site.

Of the non-FQ antibiotics, AMX exhibited a reduced risk of TR compared to no AMX in every tendon class and time window, similar to its low risk in previous studies. It exhibited a significantly lower risk in the 30, and 60-day window except for the Achilles tendon. AZM and AMC exhibited a similar benign risk in all time windows except for TR of rotator cuff in >60 days window

LEX was the surprise non-FQ antibiotic. It exhibited modest to large *increase*d TR risk at ≤30 days across all sites ranging from a low of 16% increase for complete rupture of rotator cuff to a high 114% increase for Achilles TR. Its risk was also significantly higher at each time window for all TRs taken together.

Of the FQs, CIP, the most frequently prescribed FQ, and MXF, the least frequently prescribed FQ, exhibited little to no increased risk of TR within each anatomic site and each time frame (Table 3). LVX is the only FQ to exhibit a significant *increase* in TR risk - of 16%, and 112% for rupture of rotator cuff and Achilles TR respectively in the ≤30 day window. Notably, the risk of LVX never exceeded the risk of the non-FQ, LEX in any comparison.

In a post-hoc analysis (Table 4), we compared the TR risk of each antibiotic with every other antibiotic (pairwise comparisons of FQ vs. FQ and FQ vs. non-FQ), for ≤30 day window. These results paralleled the above-mentioned risk for each study antibiotic.

Again, TR risk for LVX was greater than that of CIP, MXF, AMC, AMX, and AZM in a ≤30 day window. However, LVX risk was comparable to that of LEX for Achilles TR and rupture of rotator cuff and significantly lower than LEX for the other TR class. When comparing the risk of FQs as a class against that of non-FQ antibiotics, most of the non-FQ antibiotics had significantly greater risk than the FQ class as a whole across all TR sites.

Discussion

Our results conflict with the common assertion that the Achilles tendon rupture is the most common, up to 90% of tendon ruptures.[35] In our elderly cohort, Achilles TRs were a tiny proportion (2.9 %) of all ruptures. Some of this difference may be explained by the differences in demographics. Reports of high prevalence of Achilles TR came from studies of young military populations.[36,37] In contrast, our data came from an elderly Medicare population. Some of the difference could also be due to less ability to diagnose non-Achilles tendon ruptures without 3D joint imaging.

Many authorities describe the relationship between FQs and TRs as a class "effect". However, FQs as a class had no significant risk of TR compared with each of the three non-FQ antibiotics in any time window. Further, neither MXF (n= 23,207 subjects) nor CIP (n=314,864 subjects), the oral FQ with the greatest use and with a greater effect on metalloproteases than other FQs,[38–40] had any TR risk at any anatomic site in any time window. CIP's lack of risk is consistent with two studies[5,9] in which CIP exhibited zero risk or small risks compared to ofloxacin, a racemic mixture whose active ingredient

is the levo-isomer, LVX. We do see a strong association between LVX and TRs whether we used no LVX or three of the non-FQ antibiotics as controls. However, with LEX, the one cephalosporin as comparator, this association disappears.

One previous study described the effect of FQs on TR risk as small and unimportant.[10] Two studies reported no effect of FQs on TR risk.[9,11] At least 7 previous observational studies reported increased risks of TR after the use of FQ.[3–8,12] However, in all but one study, the TR event rates were very low (between 5 and 111) among patients taking an FQ. In comparison, our study included 17,949 (4.1%) such patients. One previous study did report a large number of events, 23,000 (3.5%) patients with TRs while on FQs and, like our study, it also focused exclusively on elderly patients.[3] However, it did not compare FQ use against no FQ use (but against times when FQ's were used and not used in one patient population so they could not adjust for the different levels of clinical attention at visits requiring a systemic antibiotic vs visits that did not). Furthermore, they assessed the association between AMX and TRs in separate analysis and used the risk of TRs in that analysis as the comparator for the risk observed in the FQ analysis. But AMX treated patients are likely at much lower acuity level (per our data) introducing large possible differential biases into that comparison. Furthermore, their analysis did not include death as a competing risk as is recommend when death rates exceed event rates.[23] They reported no death rates, but death rates in their study likely exceeded their event rates given the similarity of their population with ours.

According to our data, the AMX treated patients had fewer comorbidities (as was also true in Daneman's study), almost 14% fewer hospitalizations and half of death rate per 1000 patient-years, compared to patients taking LVX. So the two populations are not comparable. LVX appears to be reserved for more severe infections or more fragile patients and thus subject to differential biases.

The reported activation of metalloprotease activity by FQs has underpinned the idea of a causal link between FQs and TRs. The argument goes as follows: FQs stimulate metalloproteases, which can break down collagen; the tendon is made of collagen; so FQs may cause TRs. However, our data disrupts this argument. CIP which strongly *stimulates* MMP activity,[17,18] exhibited *no* risk of TRs in our study, and LEX which *inhibits* MMP activity[41,42] exhibited a *large* risk. So we have to question whether metalloprotease activity has any relevance to TR risk, and consider other explanations for the observed associations.

The indication for an antibiotic is a presumed bacterial infection. The reported associations between antibiotics and TR could be consequence of the indication rather than the antibiotic itself and be an example of the confounding by indication bias.[43] Such a bias could explain many reported associations between drugs and TR risk including associations with non-antibiotic drugs reported by Nyyssönen.[8]

This bias could manifest in two ways. First, that the bacterial infection might directly increase the risk of TR via stimulation of general immune or cytokine responses, or by

bacterial invasion. A recent study found gram-positive bacteria in a major share of ruptured tendons but not in "control" tendons removed surgically for grafting,[44] giving some plausibility to this hypothesis.

Secondly, the greater clinical attention likely focused on patients needing systemic antibiotics, especially those with severe infections, could increase the chance of noticing and documenting a pre-existing TR. Furthermore, a reservoir of such cases is likely to exist, because patients do not necessarily correctly identify joint and extremity symptoms as TRs and seek immediate care for them. Tendon ruptures of the shoulder capsule, for example, are notorious for developing symptoms slowly over 2-3 years[45] before being correctly diagnosed. Even Achilles tendon ruptures, can be missed (in 30% of cases) at the first presentation.[46] Seeger et al. reviewed the medical records of patients with an insurance claim reporting TRs following antibiotic use and found that nearly half of the TRs recorded in the claims were either something else (e.g., Bursa inflammation miscoded as a TR) or the chart had occurred before the antibiotic use but only seen in a claim after antibiotic use.[11]

We cannot conclude that confounding by indication fully explains the observed TR associations with LEX and LVX, but they are candidates that should be considered before we rush to causal judgements about such associations.

Limitation

This study faces all of the limitations of observational studies. Furthermore, it applies only to fee-for-service Medicare populations. In addition, we had no options to verify claims diagnoses via chart review.

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Figure 1. Consort Diagram

Table 1. Outcome, Medical/Medication Use, Diseases and Patient Characteristics by Type of Antibiotics

VARIABLE	Overall	FLQ	CIP	LVX	MXF	AMX	AZM	LEX	AMC	None
N	1,186,013	438,387	314,864	216,796	23,207	340,814	412,465	259,720	243,470	358,966
Any Tendon rupture	44,098(3.7)	17,949(4.1)	12,715(4.0)	8,774(4.0)	1,308(5.6)	13,666(4.0)	17,813(4.3)	11,397(4.4)	9,665(4.0)	10,665(3.0)
Death	58,947(5.0)	32,523(7.4)	21,093(6.7)	21,057(9.7)	3,458(14.9)	13,801(4.0)	21,130(5.1)	16,262(6.3)	14,315(5.9)	14,524(4.0)
Censored at HMO entry	148,155(12.5)	38,486(8.8)	27,619(8.8)	16,383(7.6)	2,525(10.9)	29,169(8.6)	36,628(8.9)	20,758(8.0)	18,087(7.4)	67,111(18.7)
Censored at disenrollment	163(0.0)	30(0.0)	16(0.0)	16(0.0)	2(0.0)	26(0.0)	32(0.0)	26(0.0)	24(0.0)	86(0.0)
Censored at DEC 31 2016	934,650(78.8)	349,399(79.7)	253,421(80.5)	170,566(78.7)	15,914(68.6)	284,152(83.4)	336,862(81.7)	211,277(81.3)	201,379(82.7)	266,580(74.3)
Years of follow-up, median(total)	3.7(4,736,653)	4.4(2,108,848)	4.6(1,558,932)	4.6(1,071,395)	5.8(134,098)	4.3(1,642,127)	4.4(1,993,833)	4.7(1,301,503)	4.4(1,180,082)	2.4(1,068,045)
Tendon ruptures in 1000 person-year	9.31	8.51	8.16	8.19	9.75	8.32	8.93	8.76	8.19	9.99
Death in 1000 person-years	12.44	15.42	13.53	19.65	25.79	8.40	10.60	12.49	12.13	13.60
Female	686,191(57.9)	268,614(61.3)	199,875(63.5)	127,986(59.0)	14,203(61.2)	202,687(59.5)	262,764(63.7)	153,714(59.2)	145,039(59.6)	192,297(53.6)
White	962,892(81.2)	368,022(83.9)	263,797(83.8)	184,123(84.9)	19,830(85.4)	284,057(83.3)	347,625(84.3)	223,266(86.0)	208,962(85.8)	273,667(76.2)
Black	86,160(7.3)	25,870(5.9)	18,496(5.9)	11,820(5.5)	1,395(6.0)	20,007(5.9)	22,779(5.5)	12,447(4.8)	12,188(5.0)	35,414(9.9)
Hispanic	65,120(5.5)	22,403(5.1)	16,681(5.3)	10,800(5.0)	960(4.1)	16,221(4.8)	19,561(4.7)	11,884(4.6)	10,514(4.3)	24,719(6.9)
Asian	30,361(2.6)	9,596(2.2)	7,040(2.2)	4,264(2.0)	542(2.3)	9,856(2.9)	10,391(2.5)	4,679(1.8)	4,574(1.9)	10,506(2.9)
Other	41,480(3.5)	12,496(2.9)	8,850(2.8)	5,789(2.7)	480(2.1)	10,673(3.1)	12,109(2.9)	7,444(2.9)	7,232(3.0)	14,660(4.1)
Ever dual	190,474(16.1)	72,592(16.6)	51,951(16.5)	39,324(18.1)	4,613(19.9)	47,213(13.9)	60,955(14.8)	42,048(16.2)	34,847(14.3)	67,807(18.9)
Non-dual LIS	30,839(2.6)	10,048(2.3)	7,233(2.3)	5,077(2.3)	589(2.5)	6,865(2.0)	8,985(2.2)	5,564(2.1)	5,122(2.1)	12,821(3.6)
Non-dual no LIS	964,700(81.3)	355,747(81.1)	255,680(81.2)	172,395(79.5)	18,005(77.6)	286,736(84.1)	342,525(83.0)	212,108(81.7)	203,501(83.6)	278,338(77.5)
Living in rural area	269,718(22.7)	105,600(24.1)	76,431(24.3)	54,376(25.1)	4,632(20.0)	78,183(22.9)	97,183(23.6)	66,881(25.8)	57,690(23.7)	77,621(21.6)
Days on RX, median(IQR)	N/A	N/A	10.0(7.0-20.0)	10.0(7.0-20.0)	10.0(7.0-14.0)	10.0(7.0-20.0)	6.0(5.0-15.0)	10.0(7.0-17.0)	10.0(10.0-20.0)	N/A
Hospitalization	349,959(29.5)	198,846(45.4)	142,538(45.3)	113,829(52.5)	14,002(60.3)	132,304(38.8)	156,185(37.9)	119,209(45.9)	103,515(42.5)	51,525(14.4)
Outpatient visits per year, median(IQR)	19.6(11.1-33.0)	27.1(17.2-42.7)	27.3(17.5-42.9)	30.1(19.0-47.8)	34.0(21.7-53.7)	23.6(14.5-37.5)	24.6(15.5-38.8)	27.5(17.2-43.2)	26.6(16.7-42.2)	12.3(6.0-21.8)
AMI	25,822(2.2)	13,365(3.0)	9,219(2.9)	8,126(3.7)	1,075(4.6)	8,592(2.5)	10,974(2.7)	8,329(3.2)	7,242(3.0)	5,103(1.4)
Atrial Fibrillation	88,563(7.5)	43,513(9.9)	30,171(9.6)	25,198(11.6)	3,187(13.7)	32,510(9.5)	36,148(8.8)	29,866(11.5)	26,056(10.7)	16,536(4.6)
Cataract	559,583(47.2)	244,465(55.8)	179,419(57.0)	122,945(56.7)	14,520(62.6)	189,761(55.7)	232,931(56.5)	148,677(57.2)	136,980(56.3)	125,610(35.0)
Chronic Kidney Disease	221,890(18.7)	116,699(26.6)	85,372(27.1)	65,142(30.0)	7,467(32.2)	73,023(21.4)	90,452(21.9)	68,947(26.5)	60,172(24.7)	43,467(12.1)
COPD	172,328(14.5)	103,941(23.7)	65,202(20.7)	71,669(33.1)	10,259(44.2)	58,641(17.2)	96,369(23.4)	54,994(21.2)	55,940(23.0)	23,222(6.5)
Heart Failure	129,993(11.0)	72,127(16.5)	49,366(15.7)	45,112(20.8)	6,216(26.8)	45,517(13.4)	58,766(14.2)	44,275(17.0)	38,781(15.9)	22,301(6.2)
Diabetes	344,557(29.1)	154,018(35.1)	111,041(35.3)	81,644(37.7)	9,558(41.2)	109,157(32.0)	134,201(32.5)	91,923(35.4)	83,309(34.2)	82,220(22.9)
Glaucoma	179,324(15.1)	75,509(17.2)	55,889(17.8)	36,817(17.0)	4,624(19.9)	59,916(17.6)	72,717(17.6)	45,015(17.3)	41,873(17.2)	42,576(11.9)
Hip/Pelvic Fracture	9,969(0.8)	5,630(1.3)	4,169(1.3)	3,273(1.5)	458(2.0)	3,656(1.1)	4,196(1.0)	3,494(1.3)	2,734(1.1)	1,733(0.5)
Ischemic Heart Disease	326,305(27.5)	160,828(36.7)	113,815(36.1)	90,604(41.8)	11,221(48.4)	113,981(33.4)	140,977(34.2)	96,904(37.3)	88,665(36.4)	64,072(17.8)
Depression	263,154(22.2)	131,795(30.1)	96,524(30.7)	71,887(33.2)	8,813(38.0)	91,018(26.7)	116,614(28.3)	79,419(30.6)	73,001(30.0)	49,814(13.9)
Alzheimer's Disease Or Senile Dementia	47,984(4.0)	26,582(6.1)	19,523(6.2)	15,387(7.1)	1,937(8.3)	15,125(4.4)	19,170(4.6)	16,083(6.2)	12,919(5.3)	9,593(2.7)
Osteoporosis	131,554(11.1)	64,596(14.7)	48,633(15.4)	33,271(15.3)	4,594(19.8)	46,862(13.8)	60,466(14.7)	37,260(14.3)	34,276(14.1)	25,391(7.1)
Rheumatoid Arthritis/Osteoarthritis	457,256(38.6)	219,767(50.1)	161,736(51.4)	114,796(53.0)	13,468(58.0)	171,692(50.4)	204,700(49.6)	138,911(53.5)	123,436(50.7)	82,578(23.0)
Stroke/Transient Ischemic Attack	72,098(6.1)	37,348(8.5)	27,127(8.6)	21,120(9.7)	2,665(11.5)	24,161(7.1)	30,139(7.3)	22,711(8.7)	19,678(8.1)	14,528(4.0)
Breast Cancer	55,748(4.7)	26,507(6.0)	19,726(6.3)	13,536(6.2)	1,548(6.7)	18,343(5.4)	24,234(5.9)	17,211(6.6)	14,315(5.9)	11,119(3.1)

Colorectal Cancer	19,288(1.6)	9,912(2.3)	7,248(2.3)	5,509(2.5)	592(2.6)	5,739(1.7)	7,054(1.7)	5,494(2.1)	4,875(2.0)	4,186(1.2)
Prostate Cancer	44,960(3.8)	25,817(5.9)	20,459(6.5)	12,558(5.8)	972(4.2)	14,604(4.3)	15,726(3.8)	12,260(4.7)	10,969(4.5)	8,424(2.3)
Lung Cancer	19,307(1.6)	12,412(2.8)	7,302(2.3)	8,971(4.1)	1,415(6.1)	5,539(1.6)	9,454(2.3)	5,617(2.2)	6,079(2.5)	2,900(0.8)
Endometrial Cancer	9,025(0.8)	4,636(1.1)	3,594(1.1)	2,299(1.1)	267(1.2)	2,860(0.8)	3,605(0.9)	2,653(1.0)	2,191(0.9)	1,872(0.5)
Anemia	379,500(32.0)	192,157(43.8)	139,042(44.2)	105,622(48.7)	12,941(55.8)	134,693(39.5)	163,370(39.6)	112,491(43.3)	101,770(41.8)	72,066(20.1)
Asthma	116,515(9.8)	69,444(15.8)	44,946(14.3)	46,600(21.5)	7,161(30.9)	41,571(12.2)	69,541(16.9)	37,221(14.3)	39,249(16.1)	13,935(3.9)
Hyperlipidemia	824,020(69.5)	343,365(78.3)	248,590(79.0)	172,542(79.6)	19,239(82.9)	263,142(77.2)	320,295(77.7)	203,560(78.4)	190,838(78.4)	202,679(56.5)
Hyperplasia	147,478(12.4)	78,374(17.9)	59,791(19.0)	39,048(18.0)	3,968(17.1)	51,492(15.1)	56,331(13.7)	41,857(16.1)	38,373(15.8)	27,598(7.7)
Hypertension	812,062(68.5)	340,354(77.6)	244,672(77.7)	174,349(80.4)	19,336(83.3)	255,879(75.1)	310,348(75.2)	202,254(77.9)	186,560(76.6)	203,427(56.7)
Hypothyroidism	241,371(20.4)	111,526(25.4)	81,897(26.0)	57,796(26.7)	6,854(29.5)	81,135(23.8)	104,685(25.4)	65,755(25.3)	61,689(25.3)	50,607(14.1)
Anxiety Disorders	188,338(15.9)	99,450(22.7)	72,980(23.2)	55,437(25.6)	6,837(29.5)	68,299(20.0)	88,527(21.5)	58,896(22.7)	54,366(22.3)	32,009(8.9)
Bipolar Disorder	22,352(1.9)	11,667(2.7)	8,668(2.8)	6,596(3.0)	816(3.5)	7,570(2.2)	9,470(2.3)	7,267(2.8)	6,113(2.5)	4,295(1.2)
Major Depressive Affective Disorder	192,927(16.3)	100,587(22.9)	73,797(23.4)	55,907(25.8)	7,005(30.2)	68,188(20.0)	87,366(21.2)	61,097(23.5)	55,544(22.8)	34,020(9.5)
Schizophrenia and Other Psychotic Disorders	20,889(1.8)	11,859(2.7)	8,718(2.8)	7,097(3.3)	911(3.9)	6,173(1.8)	7,989(1.9)	7,130(2.7)	5,496(2.3)	4,390(1.2)
Epilepsy	19,882(1.7)	10,315(2.4)	7,476(2.4)	6,039(2.8)	700(3.0)	5,922(1.7)	7,690(1.9)	6,218(2.4)	5,063(2.1)	4,263(1.2)
Cystic Fibrosis and Metabolic Disorders	12,209(1.0)	6,270(1.4)	4,671(1.5)	3,448(1.6)	445(1.9)	4,394(1.3)	5,473(1.3)	3,738(1.4)	3,370(1.4)	2,196(0.6)
Fibromyalgia, Chronic Pain and Fatigue	210,878(17.8)	111,190(25.4)	81,838(26.0)	61,637(28.4)	7,420(32.0)	78,553(23.0)	99,990(24.2)	68,291(26.3)	62,553(25.7)	34,163(9.5)
Viral Hepatitis (general)	14,494(1.2)	6,408(1.5)	4,462(1.4)	3,602(1.7)	443(1.9)	4,281(1.3)	5,155(1.2)	3,715(1.4)	3,326(1.4)	3,780(1.1)
Liver Disease Cirrhosis and other liver conditions	78,506(6.6)	43,855(10.0)	32,340(10.3)	24,720(11.4)	3,136(13.5)	27,186(8.0)	34,311(8.3)	24,344(9.4)	22,635(9.3)	13,593(3.8)
Leukemias and Lymphomas	17,825(1.5)	10,263(2.3)	6,948(2.2)	6,633(3.1)	882(3.8)	6,154(1.8)	8,393(2.0)	5,665(2.2)	5,745(2.4)	2,799(0.8)
Migraine and other chronic headache	40,625(3.4)	21,449(4.9)	16,251(5.2)	11,461(5.3)	1,485(6.4)	15,458(4.5)	20,000(4.8)	12,746(4.9)	12,337(5.1)	6,453(1.8)
Mobility Impairments	25,125(2.1)	13,568(3.1)	9,989(3.2)	7,900(3.6)	926(4.0)	7,313(2.1)	9,063(2.2)	8,158(3.1)	6,350(2.6)	5,596(1.6)
Obesity	227,801(19.2)	108,503(24.8)	78,347(24.9)	58,906(27.2)	6,536(28.2)	79,851(23.4)	96,219(23.3)	68,680(26.4)	61,392(25.2)	45,069(12.6)
Peripheral Vascular Disease	112,814(9.5)	62,250(14.2)	44,377(14.1)	37,004(17.1)	4,875(21.0)	39,571(11.6)	50,623(12.3)	39,277(15.1)	33,794(13.9)	18,709(5.2)
Tobacco Use Disorders	124,413(10.5)	61,579(14.0)	39,941(12.7)	38,193(17.6)	4,862(21.0)	37,089(10.9)	52,063(12.6)	34,177(13.2)	32,020(13.2)	27,318(7.6)
Pressure Ulcers and Chronic Ulcers	39,536(3.3)	24,923(5.7)	18,268(5.8)	15,406(7.1)	1,988(8.6)	12,855(3.8)	15,975(3.9)	18,878(7.3)	14,319(5.9)	5,172(1.4)
Deafness and Hearing Impairment	73,788(6.2)	37,425(8.5)	27,525(8.7)	20,022(9.2)	2,633(11.3)	28,696(8.4)	34,931(8.5)	22,986(8.9)	23,349(9.6)	11,975(3.3)

Note. Data are presented as No. (%) of patients unless otherwise noted.
Abbreviations: FLQ, fluoroquinolone; CIP, ciprofloxacin; LVX, levofloxacin; MXF, moxifloxacin; AMX, Amoxicillin; AMC, Amoxicillin Clavulanate; AZT, Azithromycin; LEX, Cephalexin; IQR, interquartile range.

Table 2. Hazard Ratios of Tendon Rupture for Each Covariate

VARIABLE	REFERENCE	HR(95% CI)
Female	Male	0.71(0.70,0.72)
Black	White	0.76(0.74,0.78)
Hispanic		0.91(0.88,0.94)
Asian		0.68(0.64,0.72)
Other		1.03(0.99,1.07)
Dual ever	Non-dual non-LIS	0.67(0.65,0.69)
Non-dual LIS		0.69(0.66,0.72)
Living in rural area	No	0.93(0.92,0.95)
Medicare part d since 2008	Medicare part D since 2007	1.04(1.00,1.07)
Medicare part d since 2009		1.13(1.09,1.17)
Medicare part d since 2010		1.19(1.15,1.23)
Medicare part d since 2011		1.23(1.19,1.27)
Medicare part d since 2012		1.19(1.15,1.23)
Medicare part d since 2013		1.13(1.09,1.17)
Medicare part d since 2013		1.17(1.13,1.22)
Medicare part d since 2015		1.08(1.03,1.12)
Medicare part d since 2016		1.29(0.47,3.55)
AMI	No	0.76(0.71,0.81)
Atrial Fibrillation	No	0.93(0.91,0.96)
Cataract	No	1.24(1.22,1.25)
Chronic Kidney Disease	No	0.91(0.89,0.93)
COPD	No	0.86(0.83,0.88)
Heart Failure	No	0.78(0.76,0.81)
Diabetes	No	0.98(0.96,0.99)
Glaucoma	No	1.11(1.09,1.13)
Hip/Pelvic Fracture	No	0.76(0.69,0.85)
Ischemic Heart Disease	No	1.11(1.09,1.12)
Depression	No	1.17(1.14,1.21)
Alzheimer's Disease or Senile Dementia	No	0.69(0.65,0.72)
Osteoporosis	No	1.04(1.02,1.06)
Rheumatoid Arthritis/Osteoarthritis	No	2.83(2.79,2.88)
Stroke/Transient Ischemic Attack	No	0.96(0.93,1.00)
Breast Cancer	No	0.94(0.91,0.97)
Colorectal Cancer	No	0.77(0.72,0.83)
Prostate Cancer	No	1.01(0.97,1.04)
Lung Cancer	No	0.39(0.35,0.44)
Endometrial Cancer	No	0.85(0.77,0.94)
Anemia	No	1.01(0.99,1.03)

Asthma	No	1.24(1.21,1.27)
Hyperlipidemia	No	1.36(1.34,1.38)
Hyperplasia	No	1.14(1.11,1.16)
Hypertension	No	1.10(1.09,1.12)
Hypothyroidism	No	1.08(1.06,1.10)
Anxiety Disorders	No	0.98(0.96,1.00)
Bipolar Disorder	No	1.02(0.96,1.08)
Major Depressive Affective Disorder	No	1.03(1.00,1.07)
Schizophrenia and Other Psychotic Disorders	No	0.66(0.61,0.72)
Epilepsy	No	0.85(0.80,0.91)
Fibromyalgia, Chronic Pain and Fatigue	No	1.39(1.36,1.41)
Viral hepatitis (general)	No	1.02(0.94,1.10)
Liver Disease Cirrhosis and other liver conditions	No	0.94(0.91,0.97)
Leukemias and Lymphomas	No	0.94(0.88,1.00)
Migraine and other chronic headache	No	1.26(1.21,1.30)
Mobility Impairments	No	0.69(0.64,0.74)
Obesity	No	1.06(1.04,1.08)
Peripheral Vascular Disease	No	1.00(0.97,1.03)
Tobacco Use Disorders	No	0.81(0.79,0.84)
Pressure Ulcers and Chronic Ulcers	No	0.81(0.77,0.85)
Deafness And Hearing Impairment	No	1.19(1.16,1.23)

Abbreviations: HR, hazard ratio, CI, confidence interval; FLQ, fluoroquinolone; CIP, ciprofloxacin; LVX, levofloxacin; MXF, moxifloxacin; AMX, Amoxicillin; AMC, Amoxicillin Clavulanate; AZT, Azithromycin; LEX, Cephalexin.

Table 3. Hazard Ratios of Each Antibiotic by Anatomic Sites and Temporal Order of Drug Exposure

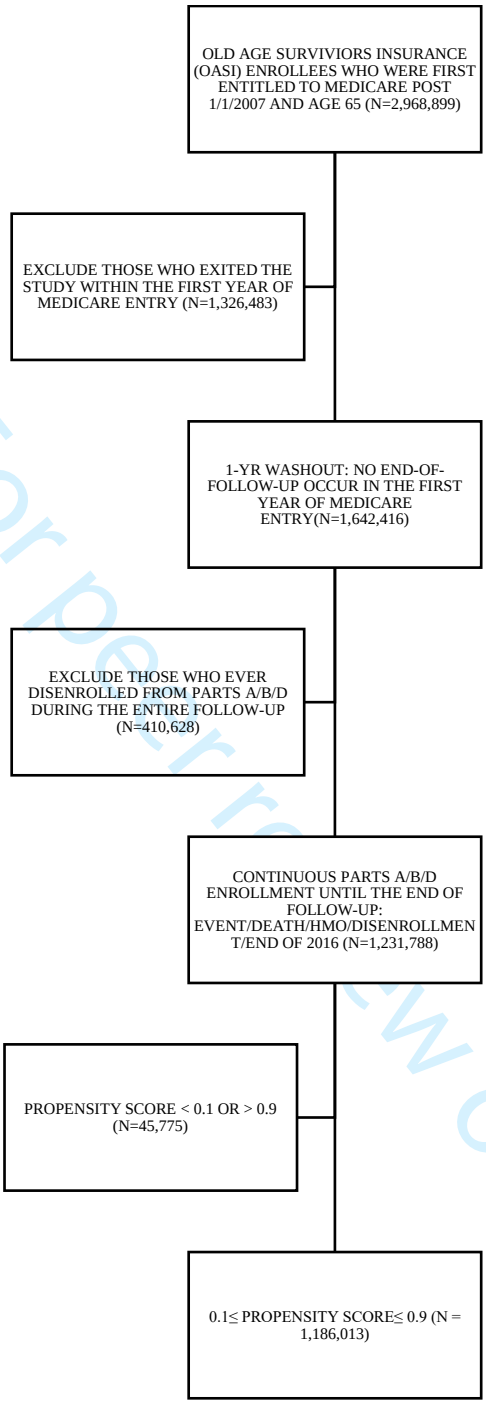
VARIABLE	REFERENCE	Any Tendon Rupture HR(95% CI)	Achilles Tendon Rupture HR(95% CI)	Complete Rupture of Rotator Cuff HR(95% CI)	Other Tendon Ruptures HR(95% CI)
Use AMX ≤ 30 days		0.87(0.82,0.92)	0.92(0.66,1.29)	0.88(0.83,0.94)	0.83(0.73,0.94)
Use AMX 31 - 60 days	No AMX	0.92(0.86,0.98)	0.79(0.52,1.20)	0.92(0.86,0.99)	0.96(0.83,1.10)
Use AMX ≥ 61 days		1.00(0.99,1.02)	0.94(0.84,1.05)	1.02(1.00,1.04)	0.97(0.93,1.01)
Use AMC 0 - 30 days		0.97(0.90,1.04)	1.28(0.88,1.85)	0.93(0.86,1.01)	1.11(0.95,1.29)
Use AMC 31 - 60 days	No AMC	1.04(0.96,1.14)	1.44(0.95,2.19)	1.03(0.94,1.13)	1.01(0.84,1.22)
Use AMC ≥ 61 days		1.06(1.04,1.08)	0.90(0.79,1.03)	1.07(1.04,1.09)	1.02(0.97,1.07)
Use AZM ≤ 30 days		1.02(0.97,1.08)	1.03(0.76,1.41)	1.03(0.97,1.09)	1.01(0.89,1.13)
Use AZM 31 - 60 days	No AZM	0.94(0.88,1.00)	0.91(0.63,1.31)	0.94(0.88,1.01)	0.97(0.85,1.11)
Use AZM ≥ 61 days		1.07(1.06,1.09)	1.05(0.95,1.16)	1.09(1.07,1.11)	1.01(0.98,1.05)
Use LEX ≤ 30 days		1.26(1.18,1.34)	2.14(1.61,2.85)	1.16(1.08,1.25)	1.67(1.48,1.88)
Use LEX 31 - 60 days	No LEX	1.09(1.01,1.18)	1.09(0.68,1.76)	1.09(1.00,1.19)	1.09(0.92,1.30)
Use LEX ≥ 61 days		1.09(1.07,1.12)	1.07(0.94,1.21)	1.09(1.07,1.11)	1.15(1.10,1.20)
Use LVX ≤ 30 days		1.15(1.07,1.23)	2.12(1.54,2.91)	1.16(1.07,1.26)	1.02(0.87,1.21)
Use LVX 31 - 60 days	No LVX	1.06(0.97,1.16)	2.12(1.46,3.09)	1.07(0.97,1.17)	0.97(0.80,1.19)
Use LVX ≥ 61 days		1.00(0.97,1.02)	1.11(0.97,1.27)	1.01(0.99,1.04)	0.95(0.90,1.00)
Use CIP ≤ 30 days		0.94(0.88,1.00)	0.88(0.61,1.28)	0.95(0.89,1.01)	0.83(0.72,0.95)
Use CIP 31 - 60 days	No CIP	0.95(0.89,1.02)	0.92(0.60,1.41)	0.95(0.88,1.03)	0.93(0.79,1.08)
Use CIP ≥ 61 days		0.96(0.94,0.98)	1.08(0.96,1.20)	0.97(0.95,0.99)	0.90(0.87,0.94)
Use MXF ≤ 30 days		0.69(0.49,0.97)	0.61(0.10,3.90)	0.55(0.36,0.85)	1.07(0.61,1.86)
Use MXF 31 - 60 days	No MXF	0.69(0.46,1.02)	0.00(0.00,0.00)	0.74(0.48,1.14)	0.44(0.16,1.21)
Use MXF ≥ 61 days		1.00(0.95,1.05)	1.18(0.89,1.56)	0.99(0.93,1.05)	1.12(1.00,1.24)

Abbreviations: HR, hazard ratio, CI, confidence interval; FLQ, fluoroquinolone; CIP, ciprofloxacin; LVX, levofloxacin; MXF, moxifloxacin; AMX, Amoxicillin; AMC, Amoxicillin Clavulanate; AZT, Azithromycin; LEX, Cephalexin.

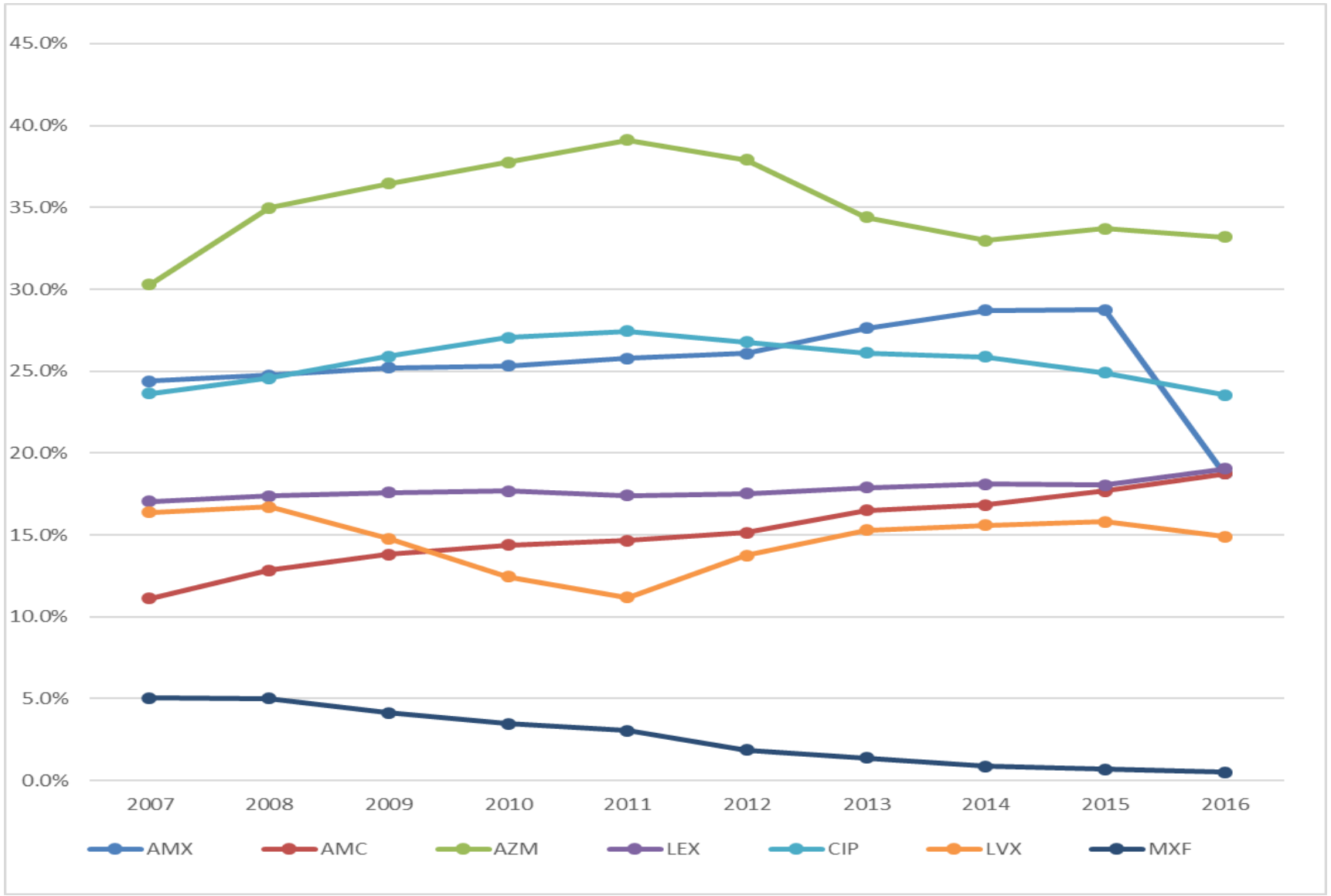
Table 4. Pairwise Comparisons

COMPARISON	LEVEL	Any Tendon Rupture HR(95% CI)	Achilles Tendon Rupture HR(95% CI)	Complete Rupture Of Rotator Cuff HR(95% CI)	Other Tendon Rupture HR(95% CI)
CIP VS. LVX	**<= 30**	0.82(0.74,0.90)	0.42(0.25,0.69)	0.81(0.73,0.90)	0.81(0.65,1.01)
CIP VS. MXF	**<= 30**	1.36(0.96,1.92)	1.45(0.22,9.66)	1.71(1.11,2.64)	0.78(0.44,1.38)
LVX VS. MXF	**<= 30**	1.66(1.18,2.35)	3.48(0.53,22.97)	2.10(1.36,3.24)	0.96(0.53,1.71)
CIP VS. AMX	**<= 30**	1.08(0.99,1.17)	0.96(0.58,1.59)	1.08(0.98,1.18)	1.00(0.82,1.21)
CIP VS. AZM	**<= 30**	0.92(0.85,1.00)	0.86(0.53,1.37)	0.92(0.84,1.01)	0.82(0.68,0.99)
CIP VS. LEX	**<= 30**	0.74(0.68,0.81)	0.41(0.26,0.66)	0.82(0.74,0.90)	0.50(0.41,0.60)
CIP VS. AMC	**<= 30**	0.97(0.88,1.07)	0.69(0.41,1.17)	1.02(0.91,1.13)	0.75(0.61,0.92)
LVX VS. AMX	**<= 30**	1.32(1.20,1.45)	2.29(1.44,3.64)	1.32(1.19,1.46)	1.23(0.99,1.52)
LVX VS. AZM	**<= 30**	1.13(1.03,1.23)	2.05(1.32,3.19)	1.13(1.02,1.25)	1.01(0.82,1.25)
LVX VS. LEX	**<= 30**	0.91(0.83,1.00)	0.99(0.64,1.53)	1.00(0.90,1.12)	0.61(0.50,0.75)
LVX VS. AMC	**<= 30**	1.19(1.07,1.32)	1.66(1.02,2.69)	1.25(1.11,1.40)	0.92(0.74,1.15)
MXF VS. AMX	**<= 30**	0.79(0.56,1.12)	0.66(0.10,4.35)	0.63(0.41,0.97)	1.29(0.73,2.28)
MXF VS. AZM	**<= 30**	0.68(0.48,0.95)	0.59(0.09,3.90)	0.54(0.35,0.83)	1.06(0.60,1.87)
MXF VS. LEX	**<= 30**	0.55(0.39,0.77)	0.28(0.04,1.86)	0.48(0.31,0.73)	0.64(0.36,1.13)
MXF VS. AMC	**<= 30**	0.71(0.51,1.01)	0.48(0.07,3.19)	0.59(0.38,0.92)	0.96(0.54,1.72)
FLQ VS. AMX	**<= 30**	1.04(0.91,1.18)	1.13(0.55,2.33)	0.96(0.82,1.13)	1.16(0.92,1.48)
FLQ VS. AZM	**<= 30**	0.89(0.78,1.01)	1.01(0.50,2.06)	0.83(0.70,0.97)	0.96(0.76,1.21)
FLQ VS. LEX	**<= 30**	0.72(0.63,0.82)	0.49(0.24,0.98)	0.73(0.62,0.86)	0.58(0.46,0.73)
FLQ VS. AMC	**<= 30**	0.94(0.82,1.08)	0.82(0.39,1.72)	0.91(0.77,1.08)	0.87(0.68,1.12)

Abbreviations: HR, hazard ratio, CI, confidence interval; FLQ, fluoroquinolone; CIP, ciprofloxacin; LVX, levofloxacin; MXF, moxifloxacin; AMX, Amoxicillin; AMC, Amoxicillin Clavulanate; AZT, Azithromycin; LEX, Cephalexin.



Supplementary Figure. Trend in Study Antibiotic Use



STROBE Statement—Checklist of items that should be included in reports of ***case-control studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	6
		(*b*) For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	8-9
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-9
		(*b*) Describe any methods used to examine subgroups and interactions	n/a
		(*c*) Explain how missing data were addressed	n/a
		(*d*) If applicable, explain how matching of cases and controls was addressed	n/a
		(*e*) Describe any sensitivity analyses	n/a
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	9
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9-10
		(b) Indicate number of participants with missing data for each variable of interest	n/a
Outcome data	15*	Report numbers in each exposure category, or summary measures of exposure	10

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-14
		(*b*) Report category boundaries when continuous variables were categorized	12-13
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14-17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

*Give information separately for cases and controls.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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The association between Tendon Ruptures and Use of Fluoroquinolone, and other oral antibiotics: A 10-year Prospective Study of 1 million U.S. senior Medicare beneficiaries

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The association between Tendon Ruptures and Use of Fluoroquinolone, and other oral antibiotics: A 10-year Prospective Study of 1 million U.S. senior Medicare beneficiaries

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3609 Words (4000 MAX)

Abstract (Max 300 words, 286 now)

Objectives: To assess the association of fluoroquinolone use with tendon ruptures compared to no fluoroquinolone and that of the four most commonly prescribed non-fluoroquinolone antibiotics in the US.

Design: Prospective observational study.

Setting: U.S. senior enrolled in the federal old-age, survivor's insurance program.

Participants: 1,009,925 Medicare fee-for-service beneficiaries and their inpatient, outpatient, prescription drug records were used.

Interventions: Seven oral antibiotics, fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin) and amoxicillin, amoxicillin-clavulanate, azithromycin and cephalexin.

Primary and Secondary Outcome measures: All tendon ruptures combined, and three types of tendon ruptures by anatomic site, Achilles tendon rupture, rupture of rotator cuff and tendon ruptures on other anatomic sites.

Results: Of three fluoroquinolones, only levofloxacin exhibited a significant increased risk of tendon ruptures - 16%, and 120% for rotator cuff and Achilles tendon rupture respectively in the ≤30 day window. Ciprofloxacin and moxifloxacin exhibited little to no increased risk of tendon ruptures. Notably, the risk of levofloxacin never exceeded the risk of the non-fluoroquinolone, cephalexin in any comparison.

Among the non-fluoroquinolone antibiotics, amoxicillin, amoxicillin-clavulanate, and azithromycin exhibited none to benign risk of tendon rupture. Cephalexin exhibited modest to large *increased* risk of tendon rupture at ≤30 day window across all anatomic rupture sites.

Conclusions: In our study, fluoroquinolones as a class were not associated with the increased risk of tendon ruptures. Neither ciprofloxacin nor moxifloxacin exhibited any risk for tendon ruptures. Levofloxacin did exhibit significant increased risk. Cephalexin with no reported effect on metalloprotease activity had an equal or greater risk than levofloxacin; so we question whether metalloprotease activity has any relevance to observed associations with tendon rupture. Confounding by indication bias may be more relevant and should be given more consideration as explanation for significant associations in observational studies of tendon rupture.

Strengths and limitations of this study

- We conducted a large (more than 1 million US senior subjects) prospective study of outpatient prescription drug records to assess the association between the use of fluoroquinolones and the occurrence of tendon ruptures compared to the most commonly used non-fluoroquinolone oral antibiotics.
- Our study included all oral fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin) prescribed in the US and the four most commonly prescribed non-fluoroquinolone antibiotics: amoxicillin, amoxicillin-clavulanate, azithromycin and cephalexin as controls.
- In addition to reporting the risk of any tendon rupture, we also reported the risk of three types of tendon ruptures by anatomic site 1) Achilles tendon rupture, 2) rupture of rotator cuff and 3) tendon ruptures on other anatomic sites as separate outcomes.
- This study is possibly only applicable to U.S. senior, aged 65 or more, Medicare fee-for-service beneficiaries.
- We had no options to verify claims diagnoses via chart review.

Introduction

Fluoroquinolones (FQ) are among the most widely prescribed antibiotics in the outpatient setting[1,2] due to their broad spectrum treatment of bacteria found in respiratory, urinary, joint, and skin infections. Several observational studies have reported the association between the use of FQs and tendinitis and tendon rupture (TR), especially of the Achilles tendon[3–12] and the U.S. Food and Drug Administration (FDA) issued black box warnings to FQ antibiotics beginning in 2008.[13] The warning was updated in 2016 to recommend using alternative antibiotics when possible.[14,15] The fact that FQs upregulate the production of metalloproteinase (MMP) enzymes with collagenase activity that could weaken tendons is taken as a mechanism to explain this reported risk.[16–18]

Studies that reported association between FQ use and TR used one or more other antibiotics as controls. One study compared the FQ rupture rates with patients using azithromycin, the most frequently used oral antibiotic in the US. Only two focused principally on TR risk among the elderly. None compared TR rates of *FQs* with those of cephalexin -- the 3rd most commonly prescribed oral antibiotic in the US.

The Virtual Research Data Center (VRDC) of Center for Medicare and Medicaid Services (CMS)[19] carries more than 10 years of Medicare claims, which include information about the usage of prescription drugs and encounter diagnoses (including tendon ruptures). It also carries information about 42 major chronic diseases, demographic characteristic and vital status. We conducted a large observational study using the VRDC to assess the association of FQ antibiotics with TR compared to that of

the four most commonly prescribed non-FQ antibiotics in the US. Here we report the results of that analysis.

Methods

Patient and public involvement

Neither patients nor the public were not involved in the design of the study.

Study population

We derived our study population from a 20% random sample of Medicare prescription drug coverage (Part D) fee-for-service enrollees who first enrolled in the Medicare under old age and survivors insurance within a month of age 65 (779-781 month-old) and on or after 1/1/2007 - the first full year of Part D prescriptions availability. We included claim data through 12/31/2016, the end of VRDC claim data available to us. All of the VRDC data is de-identified and researchers must perform all of their analysis within the VRDC computer systems, and can only pull statistical results from it.[19] We obtained approvals for these studies from the CMS privacy board and NIH OHSRP as not human subject studies.

We required subjects to be continuously enrolled in hospital insurance (Part A) and medical insurance (Part B) to assure we had full outpatient and inpatient claims data, which are not available for nearly 20% of patients with Part D only.[20] To obtain a cohort of new TR patients, we excluded (washed out) individuals with TRs recorded in the first year of their Medicare entitlement.[21] In order to assure sufficient follow-up,

we excluded patients with less than 1-year follow-up. Moreover, to obtain incident (or new) drug user cohort, we excluded individuals who were prescribed any study antibiotics during their first 3-month after Part D enrollment, while ignoring the data during the same time window for patients not taking study antibiotics. By doing so, we minimize survivor bias from a prevalent users (See Figure 1 Consort Diagram).

Primary Outcome

We identified patients with TR based upon International Classification of Diseases (ICD)-9-CM codes of 726.13, 727.60-727.69, and ICD-10-CM codes of M66.2, M66.3, M66.8, M66.9, and M75.1. We combined all TRs and reported them as one outcome, and report three types of TRs by anatomic site 1) Achilles tendon rupture, 2) rupture of rotator cuff and 3) TRs on other anatomic sites as separate outcomes. We focused on Achilles TR because it was the sole focus of many prior studies and on rotator cuff TR because it is the predominant TR of the elderly. We lumped the remaining as "other TRs".

Study antibiotics

As a study antibiotic, we included all three oral FQs prescribed in the US -- moxifloxacin (MXF), ciprofloxacin (CIP), levofloxacin (LVX), which is the active stereoisomer of ofloxacin. As controls, we also included the four most frequently prescribed non-FQ oral antibiotics - amoxicillin (AMX), amoxicillin clavulanate (AMC), azithromycin (AZT) and cephalexin (LEX). One of the FQs, and all four of the non-FQ, study antibiotics constituted the five most frequently used U.S. oral antibiotics in 2011.

Statistical Analysis

We analyzed each of the four TR outcomes in separate Fine-Gray competing risk regression analyses with death as the competing risk.[22,23] Patients became eligible for "the study" at their Medicare enrollment but prescription data did not become available until their Part D enrollment. We followed them from their entry in Part D (while accounting for left truncation[24]) until their death, switch to a capitated plan, disenrollment from Medicare or 12/31/2016 – whichever came first. We adjusted hazard ratio (HR) of each study antibiotic for concurrent use of other study antibiotics and adjusted for calendar year of subject's Part D entry, to account for secular trends. We also adjusted each HR for patient's characteristics, income, gender, race, rural residency (Yes/No) and also for 42 chronic conditions from the Medicare Master Beneficiary Summary File (MBSF)[25] with >1% prevalence, as a measure of overall health. Based upon monthly indicators of dual-eligibility and Low Income Subsidy (LIS) status, we separated study individuals into three groups: 1) dual whose income is <135% Federal Poverty Line (FPL); 2) non-dual LIS whose income is between 135 and 150% FPL; and non-dual no LIS whose income is >150% FPL. We used this variable in the analysis as a surrogate for economic status.[26]

We assumed that patients were on a given kind of study drug from the prescription dispensing date to the end of days of supply. We did not distinguish between different brands of a study drugs. Following the approach of prior studies,[3–5] we separated subjects by temporal exposure within each study drug, including groups for never

exposed, exposed within 30 days, 31-60 days, and >60 days of the index (or TR event) time. Thus, by this approach we could detect the presumed short term action of the FQ's on tendons and avoid the risk of non-differential misclassification that can occur with too simple (yes/no) drug exposure measures.[27] In order to minimize the immortal time bias, we treated all drug usage measures and all patients characteristics, except gender, race and rural residency, as time-varying covariates.[28,29] In order to mitigate selection bias toward use of any study antibiotics, we employed a propensity score (PS) approach.[30,31] We first derived a PS of taking any of study antibiotics as a function of patient's characteristics at the date of the first antibiotic use after Part D entry from a multiple logistic regression. We used the median days to the first study antibiotic use in patients taking study antibiotics as the cutoff time for subjects not taking study antibiotics. We performed our analyses with an inverse propensity score weight (IPSW) excluding individuals with the PS below 0.1 and above 0.9, to mitigate poorer performance in the presence of a strong treatment-selection process.[32] In post-hoc analyses, we also compared the risk of TR of each study antibiotics to that of every other study antibiotic on a pairwise basis.

Results

Study population and Secular trend

From our 20% sample of Part D enrollees, 1,009,925 patients satisfied all our selection criteria including the washout of individuals with any antibiotic use in their first 3-month of Part D enrollment (Figure 1 Consort Diagram). Follow-up began with an individual's enrollment in Part D program (median (IQR) 0 (0-122) days from the Medicare

entitlement). We followed them for a median of 3.6 years (total 4,030,897 patient-years) until their first diagnosis of TR (3.5%), death (4.6%), switch from fee-for-service to health maintenance organization (HMO) plans (12.6%), disenrollment from Medicare (<1%) or study end on 12/31/2016 (79.3%), whichever came first. Patients had their first post enrollment claim with a diagnosis of TR at a median age of 68.5 (IQR 67.2-70.4). The proportions of non-Hispanic White, female and rural residents were 80.7%, 57.0%, and 22.6% respectively. About a fifth of patients received federal/state subsidies, i.e. Medicaid coverage on top of Medicare (dual 16.1%) or assistance in paying their Part D premium and coinsurance/copayment (non-dual LIS 2.7%). Among the 42 Medicare chronic disease covariates, hypertension (67.3%), hyperlipidemia (68.4%), cataract (46.4%), rheumatoid arthritis/osteoarthritis (36.6%), anemia (30.4%), ischemic heart disease (26.2%), and chronic kidney disease (17.9%) were the seven most prevalent (Table 1).

Of the 328,654 (33.0%) study patients who took a FQ prescription, 71.5%, 47.5% and 4.5% ever took CIP, LVX and MXF respectively. Of 576,885 (57.1%) of patients who took a non-FQ antibiotic, the figures were 53.6%, 44.9%, 33.9% and 31.1% for AZM, AMX, LEX, and AMC, respectively. Patients who took one or more study antibiotics took a median (IQR) of 3.0 (1.0-6.0) study antibiotic prescriptions and took a median (IQR) 2.0 (1.0-3.0) different study antibiotics during the observation period. About 2.5% patients who took one or more study antibiotics took more than one antibiotics at the same time.

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Secular trends in study antibiotics usage existed. MXF usage declined precipitously from 5.0% in 2007 to almost zero in 2016 – overweighting the MXF statistics for early entrants into Medicare and yielding a longer mean follow up time. CIP use hit a peak, and LVX, a nadir, in 2011. The use of AMX, AMC and LEX trended slowly upward (Supplementary Figure 1). The mode (median) of supply durations for each antibiotics were 10 (7) for AMX, 10 (10) for AMC, 5 (5) for AZM, 10 (7) for LEX, 7 (7) for CIP, 10 (7) for LVX, 10 (11) for MXF. About thirty five percent of patients were never exposed to any one of the study antibiotics during the study period.

Unadjusted figures for TR prevalence across each of the seven study antibiotic users and the no study antibiotic users ranged from a high of 5.2% for MXF to a low of 2.9% for no antibiotic (Table 1). Except for MXF, the *unadjusted* prevalence of TRs associated with each non-FQ antibiotic was *greater than* or equal to that of each FQ antibiotic. The TR rates per 1000 patient-years followed the same pattern, with the non-FQ antibiotics topping the rates of all FQs except MXF (which had the highest rate), possibly due to overweighting of MXF usage in the early years of the study. The study subjects who ever took an FQ had the highest unadjusted rate of death per 1000 person-years. LVX's death rate was nearly twice the rate of each non-FQ antibiotics. The size of the associations with diseases like diabetes, chronic renal failure and heart failure paralleled the magnitude of the death rates and was generally higher with FQs than non-FQ antibiotics (Table 1).

Primary Analysis

Table 2 presents HRs for all covariates in our Fine-Gray competing risk regression with IPSW, for all anatomic types of tendon ruptures taken together. Being a female (vs. male), African-American, Hispanic, and Asian (vs. white), being Dual or non-Dual LIS (vs. non-Dual no LIS) and living in a rural area were all associated with a *reduced* risk of tendon rupture. These risk reductions were 24% or more for all but Hispanics and rural residency covariates, and the reductions were similar across all anatomic sites. In general, life threatening chronic disease, such as AMI, COPD, heart failure and colorectal/lung/endometrial cancers were associated with a lower risk of TR in a range of 15-60% below control possibly due to constrained physical activity and/or shortened life span. Notably, diabetes and chronic renal disease, previously reported as risk factors for TR,[33,34] exhibited no increased TR risk. Mobility impairments had reduced risk of TR similar to that of the severe life threatening diseases, likely due to reduced activity. Most diseases with low life threats such as cataract, glaucoma, depression, asthma, hyperlipidemia, hypertension, prostatic hyperplasia, migraine/other chronic headache, and deafness/hearing impairment exhibited risks of 8 to 34% *above* controls probably for reasons related to longer life spans and less inhibited activity. Ischemic heart did not fit the mold of sicker equals lower TR risk. Patients with rheumatoid arthritis/osteoarthritis were a special case and had TR risk of 184% *above* control possibly due to joint and associated tendon inflammation with these disorders. Fibromyalgia/chronic pain and fatigue also exhibited a 39% increased risk of TR possibly also due to an inflammatory component.

The Achilles tendon carries the full force of the extra weight carried by obese patients and obesity was associated with a significant (13%) increase in Achilles TR ruptures while its effect on other TR classes was significant but miniscule (2-3%) (Data not shown).

Effect of antibiotics

Table 3 shows the risk associated with each study antibiotic broken down by time lag between the antibiotic use and the TR reported in a claim as well as by anatomic sites. Of the total 34,880 patients with any TR occurrence, complete rupture of rotator cuff represented the major share (80.5%), followed by other TRs (16.9%) and Achilles TR (2.6%). In the survival analysis, we followed patients until the first occurrence of TR; so, these figures count only the first TR occurrence independent of anatomic site.

Of the non-FQ antibiotics, AMX exhibited a reduced risk of TR compared to no AMX in every tendon class and time window, similar to its low risk in previous studies. It exhibited a significantly lower risk in the ≤30-day window except for the Achilles tendon. AZM and AMC exhibited a similar benign risk in all time windows except for TR of rotator cuff in >60-day window

LEX was the surprise non-FQ antibiotic. It exhibited modest to large *increase*d TR risk at ≤30-day window across all sites ranging from a low of 19% increase for complete rupture of rotator cuff to a high 93% increase for Achilles TR. Its risk was also significantly higher at ≤30-day window for all TRs taken together.

Of the FQs, CIP, the most frequently prescribed FQ, and MXF, the least frequently prescribed FQ, exhibited little to no increased risk of TR within each anatomic site and each time frame. LVX is the only FQ to exhibit a significant *increase* in TR risk - of 16%, and 120% for rupture of rotator cuff and Achilles TR respectively in the ≤30-day window. Notably, the risk of LVX never exceeded the risk of the non-FQ, LEX in any comparison.

In a post-hoc analysis (Table 4), we compared the TR risk of each antibiotic with every other antibiotic (pairwise comparisons of FQ vs. FQ and FQ vs. non-FQ), for ≤30 day window and FQs as a class vs. each non-FQ after combining the data from the three time windows. These results paralleled the above-mentioned risk for each study antibiotic in Table 3. Again, TR risk for LVX was greater than that of CIP, MXF, AMC, AMX, and AZM in a ≤30 day window. However, LVX risk was comparable to that of LEX for Achilles TR, and rupture of rotator cuff and significantly lower than LEX for the other TR class. When comparing the risk of FQs as a class against that of non-FQ antibiotics, most of the non-FQ antibiotics had significantly greater risk than the FQ class as a whole across all TR sites (See last 5 rows of Table 4).

Discussion

Our results conflict with the common assertion that the Achilles tendon rupture is the most common tendon rupture (up to 90% in one report[35]). In our elderly cohort, Achilles TRs were a tiny, 2.6%, proportion of all TRs. Some of this difference may be explained by the differences in demographics. Reports of high prevalence of Achilles TR came from studies of young military populations.[36,37] In contrast, our data came from

an elderly Medicare population. Some of the difference could also be due to less ability to diagnose non-Achilles tendon ruptures until MRI joint imaging became widely available, because such TRs are less amenable to diagnosis by physical exam.

Many authorities describe the relationship between FQs and TRs as a class "effect". However, FQs as a class had no significant risk of TR compared with each of the three non-FQ antibiotics in any time window. Further, neither MXF (n= 14,728 subjects) nor CIP (n=234,994 subjects), the oral FQ with the greatest use and with a greater effect on metalloproteases than other FQs,[38–40] had any TR risk at any anatomic site in any time window. CIP's lack of risk is consistent with two studies[5,9] in which CIP exhibited zero risk or small risks compared to ofloxacin, a racemic mixture whose active ingredient is the levo-isomer, LVX. We do see a strong association between LVX and TRs whether we used no LVX or three of the non-FQ antibiotics as controls. However, with LEX, the one cephalosporin, as comparator, this association disappears.

One previous study described the effect of FQs on TR risk as small and unimportant.[10] Two studies reported no effect of FQs on TR risk.[9,11] At least 7 previous observational studies reported increased risks of TR after the use of FQ.[3–8,12] However, in all but one study, the TR event rates were very low (between 5 and 111) among patients taking an FQ. In comparison, our study included 12,517 (3.8%) such patients. One previous study did report a large number of events, 23,000 (3.5%) patients with TRs while on FQs and, like our study, it also focused exclusively on elderly patients.[3] However, it did not compare FQ use against no FQ use (but against times when FQ's were used and not used

in one patient population so they could not adjust for the different levels of clinical attention at visits requiring a systemic antibiotic vs visits that did not). Furthermore, they assessed the association between AMX and TRs in separate analysis and used the risk of TRs in that analysis as the comparator for the risk observed in the FQ analysis. But AMX treated patients are likely at much lower acuity level (per our data) introducing large possible differential biases into that comparison. Furthermore, their analysis did not include death as a competing risk as is recommend when death rates exceed event rates.[23] They reported no death rates, but death rates in their study likely exceeded their event rates given the similarity of their population with ours.

According to our data, the AMX treated patients had fewer comorbidities (as was also true in Daneman's study), almost 14% fewer hospitalizations and half of death rate per 1000 patient-years, compared to patients taking LVX. So the two populations are not comparable. LVX appears to be reserved for more severe infections or more fragile patients and thus subject to differential biases.

The reported activation of metalloprotease activity by FQs has underpinned the idea of a causal link between FQs and TRs. The argument goes as follows: FQs stimulate metalloproteases, which can break down collagen; the tendon is made of collagen; so FQs may cause TRs. However, our data disrupts this argument. CIP which strongly *stimulates* MMP activity,[17,18] exhibited *no* risk of TRs in our study, and LEX which *inhibits* MMP activity[41,42] exhibited a *large* risk. So we have to question whether

metalloprotease activity has any relevance to TR risk, and consider other explanations for the observed associations.

The indication for an antibiotic is a presumed bacterial infection. The reported associations between antibiotics and TR could be a consequence of the indication rather than the antibiotic itself and be an example of the confounding by indication bias.[43] Such a bias could explain many reported associations between drugs and TR risk including associations with non-antibiotic drugs reported by Nyyssönen.[8]

This bias could manifest in two ways. First, that the bacterial infection might directly increase the risk of TR via stimulation of general immune or cytokine responses, or by bacterial invasion. A recent study found gram-positive bacteria in a major share of ruptured tendons but not in "control" tendons removed surgically for grafting,[44] giving some plausibility to a hypothesis that bacterial invasion associated with the infection treated by the antibiotic could be the culprit.

Secondly, the greater clinical attention likely focused on patients needing systemic antibiotics, especially those with severe infections, could increase the chance of noticing and documenting a pre-existing TR. Furthermore, a reservoir of not-yet-diagnosed such cases is likely to exist, because patients do not necessarily correctly identify joint and extremity symptoms as TRs and seek immediate care for them. Tendon ruptures of the shoulder capsule, for example, are notorious for developing symptoms slowly over 2-3 years[45] before being correctly diagnosed. Even Achilles tendon ruptures, can be missed

(in 30% of cases) at the first presentation.[46] Seeger et al. reviewed the medical records of patients with an insurance claim reporting TRs following antibiotic use and found that nearly half of the TRs recorded in the claims were either something else (e.g., Bursa inflammation miscoded as a TR) or had occurred pre antibiotic use but only seen in a claim post antibiotic use.[11]

We cannot conclude that confounding by indication fully explains the observed TR associations with LEX and LVX, but they are candidates that should be considered before we rush to causal judgements about such associations.

Limitation

This study faces all of the limitations of observational studies. Furthermore, it applies only to fee-for-service Medicare populations. In addition, we had no options to verify claims diagnoses via chart review.

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All authors have no competing interest to declare.

Contributorship Statement

SB: study conception, design, analysis and interpretation; critical review of study content; manuscript drafting; approval of the final manuscript. JL: study concept and interpretation; manuscript drafting; approval of the final manuscript. VH: study conception and interpretation; manuscript drafting; approval of the final manuscript. CJM: study conception, design and interpretation; critical review of study content; manuscript drafting; approval of the final manuscript.

Data availability

The authors confirm that the data supporting the findings of this study are available within the article [and/or] its supplementary materials.

Patient Consent for publication: Not required.

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Figure 1. Consort Diagram

Table 1. Outcome, Medical/Medication Use, Diseases and Patient Characteristics by Type of Antibiotics

Variable	Overall	FLQ	CIP	LVX	MXF	AMX	AZM	LEX	AMC	None
N	1,009,925	328,654	234,994	155,991	14,728	259,125	308,985	195,731	179,616	356,364
Tendon Rupture	34,880(3.5)	12,517(3.8)	8,811(3.7)	5,904(3.8)	770(5.2)	9,636(3.7)	12,448(4.0)	8,019(4.1)	6,622(3.7)	10,169(2.9)
Death	46,468(4.6)	23,249(7.1)	14,821(6.3)	14,610(9.4)	2,136(14.5)	9,632(3.7)	14,608(4.7)	11,394(5.8)	9,951(5.5)	13,645(3.8)
Censored at HMO entry	127,162(12.6)	27,573(8.4)	19,847(8.4)	11,142(7.1)	1,571(10.7)	21,215(8.2)	26,140(8.5)	14,887(7.6)	12,674(7.1)	65,886(18.5)
Censored at disenrollment	145(0.0)	25(0.0)	13(0.0)	13(0.0)	2(0.0)	19(0.0)	27(0.0)	23(0.0)	16(0.0)	85(0.0)
Censored at Dec 31 2016	801,270(79.3)	265,290(80.7)	191,502(81.5)	124,322(79.7)	10,249(69.6)	218,623(84.4)	255,762(82.8)	161,408(82.5)	150,353(83.7)	266,579(74.8)
Years of follow-up, median(total)	3.6(4,030,897)	4.6(1,620,894)	4.8(1,190,308)	4.8(789,849)	6.0(87,397)	4.5(1,274,357)	4.6(1,529,370)	4.8(1,000,459)	4.6(890,340)	2.5(1,067,731)
Tendon rupture, 1000 person-years	8.65	7.72	7.40	7.47	8.81	7.56	8.14	8.02	7.44	9.52
Death, 1000 person-years	11.53	14.34	12.45	18.50	24.44	7.56	9.55	11.39	11.18	12.78
Female	575,885(57.0)	197,915(60.2)	146,745(62.4)	89,682(57.5)	8,747(59.4)	151,383(58.4)	194,101(62.8)	113,308(57.9)	104,749(58.3)	191,069(53.6)
White	814,933(80.7)	274,785(83.6)	196,048(83.4)	131,725(84.4)	12,464(84.6)	215,101(83.0)	259,657(84.0)	167,825(85.7)	153,723(85.6)	271,906(76.3)
Black	75,930(7.5)	20,017(6.1)	14,286(6.1)	8,893(5.7)	956(6.5)	15,622(6.0)	17,296(5.6)	9,625(4.9)	9,199(5.1)	35,023(9.8)
Hispanic	56,582(5.6)	17,044(5.2)	12,607(5.4)	7,943(5.1)	628(4.3)	12,494(4.8)	14,805(4.8)	8,976(4.6)	7,802(4.3)	24,391(6.8)
Asian	26,336(2.6)	7,316(2.2)	5,362(2.3)	3,144(2.0)	356(2.4)	7,624(2.9)	7,945(2.6)	3,539(1.8)	3,440(1.9)	10,437(2.9)
Other	36,144(3.6)	9,492(2.9)	6,691(2.8)	4,286(2.7)	324(2.2)	8,284(3.2)	9,282(3.0)	5,766(2.9)	5,452(3.0)	14,607(4.1)
Ever Dual	162,988(16.1)	54,055(16.4)	38,277(16.3)	28,156(18.0)	2,908(19.7)	35,305(13.6)	44,940(14.5)	30,962(15.8)	25,255(14.1)	66,986(18.8)
Non-Dual LIS	26,955(2.7)	7,648(2.3)	5,459(2.3)	3,746(2.4)	385(2.6)	5,224(2.0)	6,828(2.2)	4,191(2.1)	3,818(2.1)	12,595(3.5)
Non-Dual No LIS	819,982(81.2)	266,951(81.2)	191,258(81.4)	124,089(79.5)	11,435(77.6)	218,596(84.4)	257,217(83.2)	160,578(82.0)	150,543(83.8)	276,783(77.7)
Living in rural area	228,199(22.6)	78,581(23.9)	56,385(24.0)	38,847(24.9)	2,801(19.0)	58,805(22.7)	72,282(23.4)	49,977(25.5)	42,288(23.5)	77,087(21.6)
Days on Rx, median (IQR)	N/A	N/A	10.0(7.0-20.0)	10.0(7.0-17.0)	10.0(7.0-12.0)	10.0(7.0-20.0)	5.0(5.0-11.0)	10.0(7.0-16.0)	10.0(10.0-20.0)	N/A
Hospitalization	349,959(29.5)	198,846(45.4)	142,538(45.3)	113,829(52.5)	14,002(60.3)	132,304(38.8)	156,185(37.9)	119,209(45.9)	103,515(42.5)	51,525(14.4)
Outpatient visits per year, median (IQR)	19.6(11.1-33.0)	27.1(17.2-42.7)	27.3(17.5-42.9)	30.1(19.0-47.8)	34.0(21.7-53.7)	23.6(14.5-37.5)	24.6(15.5-38.8)	27.5(17.2-43.2)	26.6(16.7-42.2)	12.3(6.0-21.8)
AMI	21,222(2.1)	9,999(3.0)	6,810(2.9)	5,862(3.8)	698(4.7)	6,474(2.5)	8,079(2.6)	6,215(3.2)	5,292(2.9)	5,012(1.4)
Atrial Fibrillation	71,635(7.1)	31,752(9.7)	21,757(9.3)	17,731(11.4)	2,028(13.8)	23,974(9.3)	26,182(8.5)	21,935(11.2)	18,764(10.4)	16,314(4.6)
Cataract	468,608(46.4)	183,870(55.9)	134,196(57.1)	88,574(56.8)	9,216(62.6)	144,455(55.7)	174,897(56.6)	112,020(57.2)	101,079(56.3)	124,931(35.1)
Chronic Kidney Disease	180,441(17.9)	86,021(26.2)	62,323(26.5)	46,121(29.6)	4,651(31.6)	53,713(20.7)	65,577(21.2)	50,361(25.7)	43,182(24.0)	42,916(12.0)
COPD	130,840(13.0)	71,913(21.9)	43,961(18.7)	48,430(31.0)	6,106(41.5)	40,109(15.5)	66,536(21.5)	37,413(19.1)	37,579(20.9)	22,739(6.4)
Heart Failure	103,010(10.2)	51,814(15.8)	34,870(14.8)	31,377(20.1)	3,776(25.6)	32,792(12.7)	41,647(13.5)	31,585(16.1)	27,223(15.2)	21,907(6.1)
Diabetes	284,919(28.2)	113,424(34.5)	81,175(34.5)	57,697(37.0)	5,942(40.3)	81,155(31.3)	98,176(31.8)	67,548(34.5)	59,984(33.4)	81,448(22.9)
Glaucoma	150,839(14.9)	56,990(17.3)	41,984(17.9)	26,603(17.1)	2,930(19.9)	45,597(17.6)	54,726(17.7)	33,936(17.3)	31,065(17.3)	42,355(11.9)
Hip/Pelvic Fracture	7,982(0.8)	4,086(1.2)	3,000(1.3)	2,289(1.5)	274(1.9)	2,673(1.0)	3,005(1.0)	2,515(1.3)	1,914(1.1)	1,689(0.5)
Ischemic Heart Disease	264,648(26.2)	117,416(35.7)	82,182(35.0)	63,659(40.8)	6,956(47.2)	83,682(32.3)	101,999(33.0)	70,612(36.1)	63,363(35.3)	63,372(17.8)
Depression	210,714(20.9)	94,554(28.8)	68,625(29.2)	49,277(31.6)	5,298(36.0)	65,642(25.3)	83,253(26.9)	56,747(29.0)	51,150(28.5)	49,320(13.8)
Alzheimer's Disease or Senile Dementia	39,132(3.9)	19,796(6.0)	14,309(6.1)	11,030(7.1)	1,206(8.2)	11,140(4.3)	13,809(4.5)	11,846(6.1)	9,309(5.2)	9,400(2.6)
Osteoporosis	106,966(10.6)	47,033(14.3)	35,217(15.0)	22,918(14.7)	2,738(18.6)	34,610(13.4)	44,016(14.2)	26,996(13.8)	24,393(13.6)	25,216(7.1)

Rheumatoid Arthritis/Osteoarthritis	369,584(36.6)	160,091(48.7)	117,018(49.8)	80,115(51.4)	8,259(56.1)	126,702(48.9)	148,653(48.1)	101,310(51.8)	88,017(49.0)	81,855(23.0)
Stroke/Transient Ischemic Attack	58,886(5.8)	27,702(8.4)	19,843(8.4)	15,051(9.6)	1,670(11.3)	17,829(6.9)	22,038(7.1)	16,684(8.5)	14,245(7.9)	14,262(4.0)
Breast Cancer	45,316(4.5)	19,362(5.9)	14,344(6.1)	9,442(6.1)	984(6.7)	13,451(5.2)	17,676(5.7)	12,543(6.4)	10,156(5.7)	11,042(3.1)
Colorectal Cancer	15,905(1.6)	7,487(2.3)	5,421(2.3)	4,048(2.6)	390(2.6)	4,304(1.7)	5,170(1.7)	4,085(2.1)	3,605(2.0)	4,104(1.2)
Prostate Cancer	37,038(3.7)	19,705(6.0)	15,577(6.6)	9,232(5.9)	643(4.4)	10,967(4.2)	11,733(3.8)	9,252(4.7)	8,070(4.5)	8,333(2.3)
Lung Cancer	14,946(1.5)	8,965(2.7)	5,144(2.2)	6,356(4.1)	905(6.1)	3,859(1.5)	6,633(2.1)	3,977(2.0)	4,267(2.4)	2,733(0.8)
Endometrial Cancer	7,396(0.7)	3,447(1.0)	2,670(1.1)	1,635(1.0)	160(1.1)	2,095(0.8)	2,637(0.9)	1,957(1.0)	1,604(0.9)	1,847(0.5)
Anemia	307,310(30.4)	140,606(42.8)	100,819(42.9)	74,308(47.6)	7,980(54.2)	99,190(38.3)	118,327(38.3)	81,967(41.9)	72,587(40.4)	71,098(20.0)
Asthma	86,120(8.5)	46,350(14.1)	29,327(12.5)	30,152(19.3)	4,091(27.8)	27,632(10.7)	46,823(15.2)	24,426(12.5)	25,465(14.2)	13,802(3.9)
Hyperlipidemia	691,148(68.4)	257,086(78.2)	185,199(78.8)	123,828(79.4)	12,162(82.6)	199,236(76.9)	239,414(77.5)	152,879(78.1)	140,364(78.1)	201,258(56.5)
Hyperplasia	122,010(12.1)	59,809(18.2)	45,517(19.4)	28,616(18.3)	2,587(17.6)	39,031(15.1)	42,070(13.6)	31,606(16.1)	28,398(15.8)	27,336(7.7)
Hypertension	679,287(67.3)	253,601(77.2)	181,231(77.1)	124,646(79.9)	12,218(83.0)	192,686(74.4)	230,409(74.6)	150,995(77.1)	136,292(75.9)	201,777(56.6)
Hypothyroidism	197,447(19.6)	81,468(24.8)	59,450(25.3)	40,372(25.9)	4,198(28.5)	59,893(23.1)	76,582(24.8)	47,973(24.5)	44,249(24.6)	50,280(14.1)
Anxiety Disorders	148,983(14.8)	70,688(21.5)	51,377(21.9)	37,563(24.1)	4,032(27.4)	48,859(18.9)	62,418(20.2)	41,655(21.3)	37,588(20.9)	31,709(8.9)
Bipolar Disorder	17,882(1.8)	8,368(2.5)	6,104(2.6)	4,533(2.9)	468(3.2)	5,442(2.1)	6,658(2.2)	5,147(2.6)	4,227(2.4)	4,242(1.2)
Major Depressive Affective Disorder	153,182(15.2)	71,732(21.8)	52,101(22.2)	38,055(24.4)	4,148(28.2)	48,846(18.9)	61,872(20.0)	43,416(22.2)	38,642(21.5)	33,660(9.4)
Schizophrenia and other Psychotic Disorders	16,764(1.7)	8,591(2.6)	6,176(2.6)	4,934(3.2)	548(3.7)	4,421(1.7)	5,597(1.8)	5,101(2.6)	3,811(2.1)	4,300(1.2)
Epilepsy	16,155(1.6)	7,543(2.3)	5,383(2.3)	4,269(2.7)	415(2.8)	4,310(1.7)	5,488(1.8)	4,510(2.3)	3,621(2.0)	4,191(1.2)
Fibromyalgia, Chronic Pain and Fatigue	166,279(16.5)	78,877(24.0)	57,494(24.5)	41,843(26.8)	4,410(29.9)	56,152(21.7)	70,667(22.9)	48,422(24.7)	43,379(24.2)	33,843(9.5)
Viral Hepatitis (General)	11,969(1.2)	4,659(1.4)	3,188(1.4)	2,523(1.6)	287(1.9)	3,156(1.2)	3,732(1.2)	2,712(1.4)	2,348(1.3)	3,735(1.0)
Liver Disease Cirrhosis and other Liver Conditions	62,675(6.2)	31,930(9.7)	23,284(9.9)	17,386(11.1)	1,919(13.0)	19,624(7.6)	24,544(7.9)	17,393(8.9)	15,958(8.9)	13,350(3.7)
Leukemias and Lymphomas	13,906(1.4)	7,228(2.2)	4,822(2.1)	4,536(2.9)	551(3.7)	4,385(1.7)	5,905(1.9)	4,025(2.1)	3,969(2.2)	2,758(0.8)
Migraine and other Chronic Headache	31,628(3.1)	14,936(4.5)	11,282(4.8)	7,520(4.8)	873(5.9)	10,841(4.2)	13,893(4.5)	8,763(4.5)	8,403(4.7)	6,419(1.8)
Mobility Impairments	20,600(2.0)	10,182(3.1)	7,356(3.1)	5,767(3.7)	577(3.9)	5,372(2.1)	6,629(2.1)	5,995(3.1)	4,610(2.6)	5,439(1.5)
Obesity	185,101(18.3)	79,130(24.1)	56,609(24.1)	41,226(26.4)	3,997(27.1)	58,654(22.6)	69,611(22.5)	49,984(25.5)	43,740(24.4)	44,772(12.6)
Peripheral Vascular Disease	90,132(8.9)	45,276(13.8)	31,866(13.6)	25,977(16.7)	3,001(20.4)	28,747(11.1)	36,241(11.7)	28,343(14.5)	23,977(13.3)	18,446(5.2)
Tobacco Use Disorders	101,890(10.1)	45,304(13.8)	28,907(12.3)	27,202(17.4)	3,042(20.7)	27,261(10.5)	37,860(12.3)	25,002(12.8)	22,975(12.8)	26,896(7.5)
Pressure Ulcers and Chronic Ulcers	30,345(3.0)	17,688(5.4)	12,800(5.4)	10,603(6.8)	1,196(8.1)	9,006(3.5)	10,926(3.5)	13,404(6.8)	9,960(5.5)	4,992(1.4)
Deafness and Hearing Impairment	59,576(5.9)	27,383(8.3)	19,976(8.5)	14,014(9.0)	1,609(10.9)	21,213(8.2)	25,498(8.3)	16,849(8.6)	16,787(9.3)	11,900(3.3)

Note. Data are presented as No. (%) of patients unless otherwise noted.
Abbreviations: FLQ, fluoroquinolone; CIP, ciprofloxacin; LVX, levofloxacin; MXF, moxifloxacin; AMX, Amoxicillin; AMC, Amoxicillin Clavulanate; AZT, Azithromycin; LEX, Cephalexin; IQR, interquartile range.

Table 2. Hazard Ratios of Tendon Rupture for Each Covariate

Variables	Reference	HR(95% CI)
Female	Male	0.70(0.69,0.72)‡
Black	White	0.76(0.73,0.78)‡
Hispanic		0.91(0.87,0.94)‡
Asian		0.67(0.63,0.71)‡
Other		1.05(1.01,1.09)†
Dual Ever	Non-Dual Non-LIS	0.66(0.64,0.68)‡
Non-Dual Lis		0.66(0.63,0.70)‡
Living In Rural Area	No	0.94(0.92,0.95)‡
Medicare Part D Since 2008	Medicare Part D Since 2007	1.03(1.00,1.07)
Medicare Part D Since 2009		1.11(1.07,1.15)‡
Medicare Part D Since 2010		1.16(1.12,1.21)‡
Medicare Part D Since 2011		1.17(1.13,1.22)‡
Medicare Part D Since 2012		1.12(1.08,1.16)‡
Medicare Part D Since 2013		1.03(1.00,1.07)
Medicare Part D Since 2013		1.05(1.01,1.09)†
Medicare Part D Since 2015		0.91(0.87,0.96)‡
Medicare Part D Since 2016		0.93(0.19,4.55)
AMI	No	0.74(0.69,0.79)‡
Atrial Fibrillation	No	0.94(0.91,0.97)‡
Cataract	No	1.23(1.21,1.25)‡
Chronic Kidney Disease	No	0.92(0.89,0.94)‡
COPD	No	0.83(0.81,0.86)‡
Heart Failure	No	0.79(0.77,0.82)‡
Diabetes	No	0.98(0.96,0.99)†
Glaucoma	No	1.10(1.08,1.12)‡
Hip/Pelvic Fracture	No	0.68(0.60,0.77)‡
Ischemic Heart Disease	No	1.10(1.08,1.12)‡
Depression	No	1.17(1.13,1.21)
Alzheimer's Disease or Senile Dementia	No	0.67(0.63,0.71)‡
Osteoporosis	No	1.03(1.01,1.06)†
Rheumatoid Arthritis/Osteoarthritis	No	2.84(2.80,2.89)‡
Stroke/Transient Ischemic Attack	No	0.97(0.94,1.01)
Breast Cancer	No	0.94(0.91,0.98)†
Colorectal Cancer	No	0.79(0.74,0.85)‡

Prostate Cancer	No	1.03(0.99,1.07)
Lung Cancer	No	0.39(0.34,0.45)‡
Endometrial Cancer	No	0.85(0.77,0.94)†
Anemia	No	1.01(0.99,1.03)
Asthma	No	1.27(1.24,1.31)‡
Hyperlipidemia	No	1.34(1.31,1.36)‡
Hyperplasia	No	1.13(1.10,1.16)‡
Hypertension	No	1.09(1.07,1.11)‡
Hypothyroidism	No	1.08(1.06,1.10)‡
Anxiety Disorders	No	0.98(0.96,1.01)
Bipolar Disorder	No	1.02(0.95,1.08)
Major Depressive Affective Disorder	No	1.06(1.02,1.10)†
Schizophrenia and Other Psychotic Disorders	No	0.67(0.61,0.74)‡
Epilepsy	No	0.83(0.77,0.90)‡
Fibromyalgia, Chronic Pain and Fatigue	No	1.39(1.36,1.42)‡
Viral Hepatitis (General)	No	1.04(0.96,1.13)
Liver Disease Cirrhosis And Other Liver Conditions	No	0.95(0.92,0.99)†
Leukemias and Lymphomas	No	0.94(0.88,1.01)
Migraine and Other Chronic Headache	No	1.28(1.23,1.33)‡
Mobility Impairments	No	0.70(0.65,0.76)‡
Obesity	No	1.04(1.02,1.06)†
Peripheral Vascular Disease	No	1.00(0.97,1.04)
Tobacco Use Disorders	No	0.82(0.80,0.85)‡
Pressure Ulcers and Chronic Ulcers	No	0.82(0.77,0.87)‡
Deafness and Hearing Impairment	No	1.21(1.17,1.25)‡

Abbreviations: HR, hazard ratio, CI, confidence interval; FLQ, fluoroquinolone; CIP, ciprofloxacin; LVX, levofloxacin; MXF, moxifloxacin; AMX, Amoxicillin; AMC, Amoxicillin Clavulanate; AZT, Azithromycin; LEX, Cephalexin.

‡ = P-value < 0.001

†= 0.001 ≤ P-value < 0.05

Table 3. Hazard Ratios of Each Antibiotic by Anatomic Sites and Temporal Order of Drug Exposure

		Any Tendon Rupture	Achilles Tendon Rupture	Complete Rupture of Rotator Cuff	Other Tendon Rupture
	Temporal Exposure	**HR(95% CI)**	**HR(95% CI)**	**HR(95% CI)**	**HR(95% CI)**
AMX VS. NO AMX	**≤ 30 days**	0.86(0.80,0.92)‡	0.88(0.59,1.33)	0.88(0.82,0.95)†	0.79(0.67,0.93)†
	31 – 60 days	0.94(0.87,1.01)	0.80(0.49,1.31)	0.91(0.84,0.99)†	1.08(0.93,1.27)
	≥ 61 days	1.00(0.98,1.02)	0.99(0.86,1.13)	1.01(0.99,1.04)	0.97(0.92,1.01)
AMC VS. NO AMC	**≤ 30 days**	0.93(0.85,1.02)	1.25(0.79,1.97)	0.87(0.79,0.97)†	1.17(0.98,1.41)
	31 – 60 days	0.95(0.85,1.05)	1.37(0.82,2.29)	0.95(0.84,1.06)	0.81(0.63,1.04)
	≥ 61 days	1.07(1.04,1.09)‡	0.95(0.81,1.12)	1.07(1.04,1.10)‡	1.02(0.96,1.08)
AZM VS. NO AZM	**≤ 30 days**	0.99(0.93,1.06)	1.15(0.82,1.63)	1.00(0.93,1.08)	0.87(0.75,1.01)
	31 – 60 days	0.90(0.84,0.98)†	0.99(0.65,1.49)	0.91(0.84,0.99)†	0.95(0.81,1.11)
	≥ 61 days	1.07(1.05,1.09)‡	1.02(0.91,1.15)	1.09(1.07,1.12)‡	0.99(0.95,1.04)
LEX VS. NO LEX	**≤ 30 days**	1.31(1.22,1.41)‡	1.93(1.35,2.75)‡	1.19(1.09,1.29)‡	1.79(1.56,2.06)‡
	31 – 60 days	1.05(0.95,1.15)	1.14(0.66,1.96)	1.06(0.96,1.18)	1.02(0.82,1.26)
	≥ 61 days	1.08(1.05,1.11)‡	1.00(0.85,1.16)	1.07(1.05,1.10)‡	1.15(1.09,1.21)‡
LVX VS. NO LVX	**≤ 30 days**	1.14(1.05,1.25)†	2.20(1.50,3.24)‡	1.16(1.06,1.28)†	0.96(0.78,1.19)
	31 – 60 days	1.09(0.98,1.21)	1.91(1.17,3.10)†	1.09(0.97,1.22)	1.14(0.90,1.43)
	≥ 61 days	1.02(1.00,1.05)	1.22(1.03,1.43)†	1.03(1.00,1.07)†	0.97(0.91,1.03)
CIP VS. NO CIP	**≤ 30 days**	0.96(0.89,1.03)	1.06(0.70,1.60)	0.96(0.88,1.04)	0.84(0.71,1.00)†
	31 – 60 days	0.92(0.85,1.01)	1.02(0.63,1.67)	0.91(0.82,1.00)†	0.95(0.78,1.14)
	≥ 61 days	0.96(0.94,0.98)‡	1.16(1.02,1.32)†	0.96(0.94,0.99)†	0.92(0.88,0.97)†
MXF VS. NO MXF	**≤ 30 days**	0.59(0.37,0.93)	0.97(0.15,6.24)	0.52(0.30,0.91)†	0.76(0.33,1.77)
	31 – 60 days	0.71(0.43,1.15)	0.00(0.00,0.00)	0.63(0.35,1.13)	0.93(0.39,2.25)
	≥ 61 days	0.99(0.93,1.06)	1.02(0.69,1.51)	0.99(0.92,1.06)	1.10(0.95,1.27)
FLQ VS. AMX	**≤ 30 days**	1.00(0.84,1.19)	1.49(0.69,3.19)	0.94(0.77,1.16)	1.08(0.77,1.50)
	31 – 60 days	0.95(0.79,1.15)	0.07(0.04,0.12)‡	0.94(0.75,1.17)	0.92(0.65,1.31)
	≥ 61 days	0.99(0.96,1.02)	1.14(0.94,1.40)	0.98(0.95,1.02)	1.03(0.96,1.11)
FLQ VS. AZM	**≤ 30 days**	0.87(0.73,1.03)	1.14(0.54,2.39)	0.83(0.68,1.02)	0.98(0.70,1.37)
	31 – 60 days	0.99(0.82,1.19)	0.06(0.04,0.09)‡	0.93(0.75,1.16)	1.06(0.75,1.49)
	≥ 61 days	0.93(0.90,0.96)‡	1.10(0.91,1.34)	0.91(0.88,0.94)‡	1.00(0.93,1.08)
FLQ VS. LEX	**≤ 30 days**	0.66(0.55,0.78)‡	0.68(0.32,1.42)	0.70(0.57,0.87)†	0.47(0.34,0.66)‡
	31 – 60 days	0.85(0.70,1.04)	0.05(0.03,0.09)‡	0.80(0.64,1.01)	0.99(0.68,1.44)
	≥ 61 days	0.92(0.89,0.95)‡	1.13(0.92,1.40)	0.92(0.89,0.96)‡	0.86(0.80,0.93)‡
FLQ VS. AMC	**≤ 30 days**	0.93(0.77,1.11)	1.05(0.48,2.32)	0.96(0.77,1.19)	0.72(0.51,1.02)
	31 – 60 days	0.94(0.77,1.15)	0.04(0.02,0.07)‡	0.90(0.72,1.14)	1.24(0.83,1.86)

≥ 61 days	0.93(0.90,0.97)‡	1.19(0.95,1.49)	0.93(0.89,0.96)‡	0.98(0.90,1.06)

Abbreviations: HR, hazard ratio, CI, confidence interval; FLQ, fluoroquinolone; CIP, ciprofloxacin; LVX, levofloxacin; MXF, moxifloxacin; AMX, Amoxicillin; AMC, Amoxicillin Clavulanate; AZT, Azithromycin; LEX, Cephalexin.

‡ = P-value < 0.001

†= 0.001 ≤ P-value < 0.05

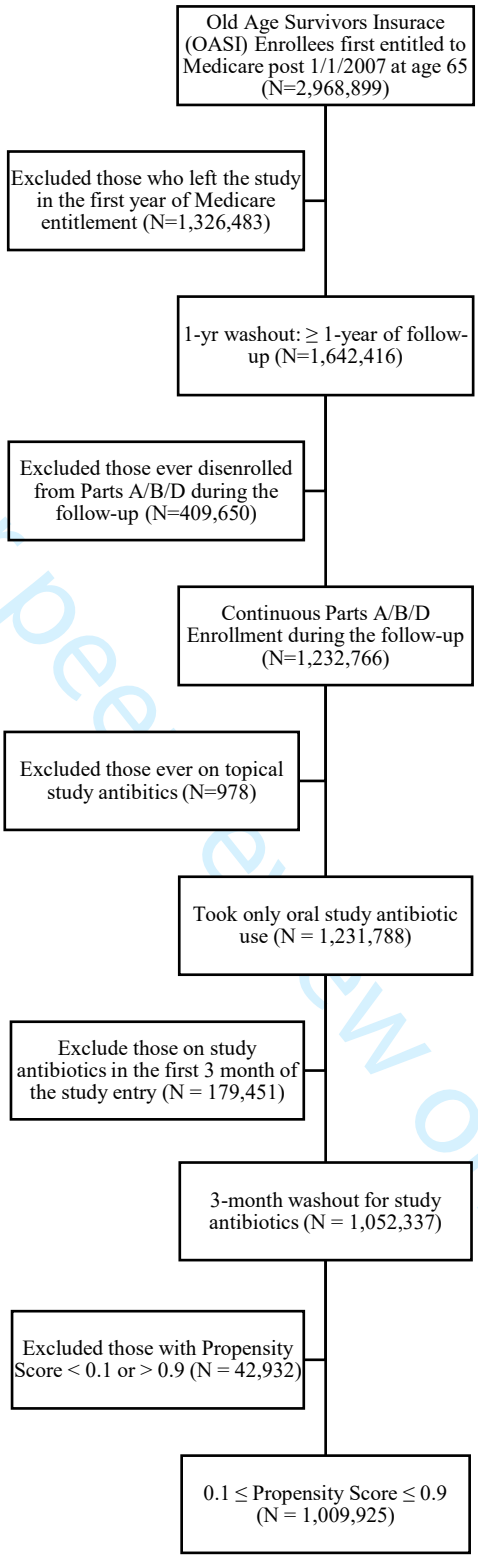
Table 4. Pairwise Comparisons

		Any Tendon Rupture	Achilles Tendon Rupture	Complete Rupture of Rotator Cuff	Other Tendon Rupture
Comparison	**Temporal Exposure**	**HR(95% CI)**	**HR(95% CI)**	**HR(95% CI)**	**HR(95% CI)**
CIP VS. LVX	**≤ 30 days**	0.84(0.75,0.94)†	0.48(0.27,0.86)†	0.82(0.73,0.94)†	0.87(0.67,1.15)
CIP VS. MXF	**≤ 30 days**	1.63(1.02,2.61)†	1.08(0.16,7.29)	1.84(1.05,3.24)†	1.10(0.47,2.60)
LVX VS. MXF	**≤ 30 days**	1.95(1.21,3.13)†	2.26(0.34,15.17)	2.24(1.27,3.94)†	1.26(0.53,3.01)
CIP VS. AMX	**≤ 30 days**	1.11(1.01,1.23)†	1.20(0.66,2.16)	1.09(0.97,1.21)	1.06(0.84,1.34)
CIP VS. AZM	**≤ 30 days**	0.97(0.87,1.06)	0.91(0.53,1.57)	0.96(0.86,1.07)	0.96(0.77,1.21)
CIP VS. LEX	**≤ 30 days**	0.73(0.66,0.81)‡	0.55(0.31,0.95)†	0.81(0.72,0.91)‡	0.47(0.37,0.59)‡
CIP VS. AMC	**≤ 30 days**	1.03(0.91,1.16)	0.84(0.46,1.56)	1.10(0.96,1.25)	0.71(0.56,0.92)†
LVX VS. AMX	**≤ 30 days**	1.33(1.19,1.49)‡	2.50(1.45,4.29)†	1.32(1.16,1.49)‡	1.22(0.93,1.59)
LVX VS. AZM	**≤ 30 days**	1.15(1.03,1.29)†	1.91(1.13,3.23)†	1.16(1.03,1.31)†	1.10(0.84,1.44)
LVX VS. LEX	**≤ 30 days**	0.87(0.78,0.98)†	1.14(0.68,1.92)	0.98(0.86,1.12)	0.54(0.41,0.69)‡
LVX VS. AMC	**≤ 30 days**	1.23(1.08,1.40)†	1.76(0.98,3.15)	1.33(1.15,1.54)‡	0.82(0.62,1.08)
MXF VS. AMX	**≤ 30 days**	0.68(0.43,1.09)	1.10(0.16,7.41)	0.59(0.34,1.03)	0.96(0.41,2.27)
MXF VS. AZM	**≤ 30 days**	0.59(0.37,0.94)†	0.84(0.13,5.65)	0.52(0.30,0.91)†	0.88(0.37,2.07)
MXF VS. LEX	**≤ 30 days**	0.45(0.28,0.72)†	0.50(0.08,3.35)	0.44(0.25,0.77)†	0.43(0.18,1.00)
MXF VS. AMC	**≤ 30 days**	0.63(0.39,1.01)	0.78(0.11,5.33)	0.60(0.34,1.05)	0.65(0.28,1.53)
FLQ VS. AMX	**Overall**	0.98(0.90,1.07)	0.49(0.36,0.68)‡	0.95(0.86,1.06)	1.01(0.86,1.19)
FLQ VS. AZM	**Overall**	0.93(0.85,1.01)	0.42(0.30,0.57)‡	0.89(0.80,0.98)†	1.01(0.86,1.19)
FLQ VS. LEX	**Overall**	0.80(0.73,0.88)‡	0.34(0.24,0.47‡	0.80(0.72,0.89)‡	0.74(0.62,0.88)‡
FLQ VS. AMC	**Overall**	0.93(0.85,1.02)	0.37(0.26,0.52)‡	0.93(0.83,1.03)	0.96(0.80,1.15)

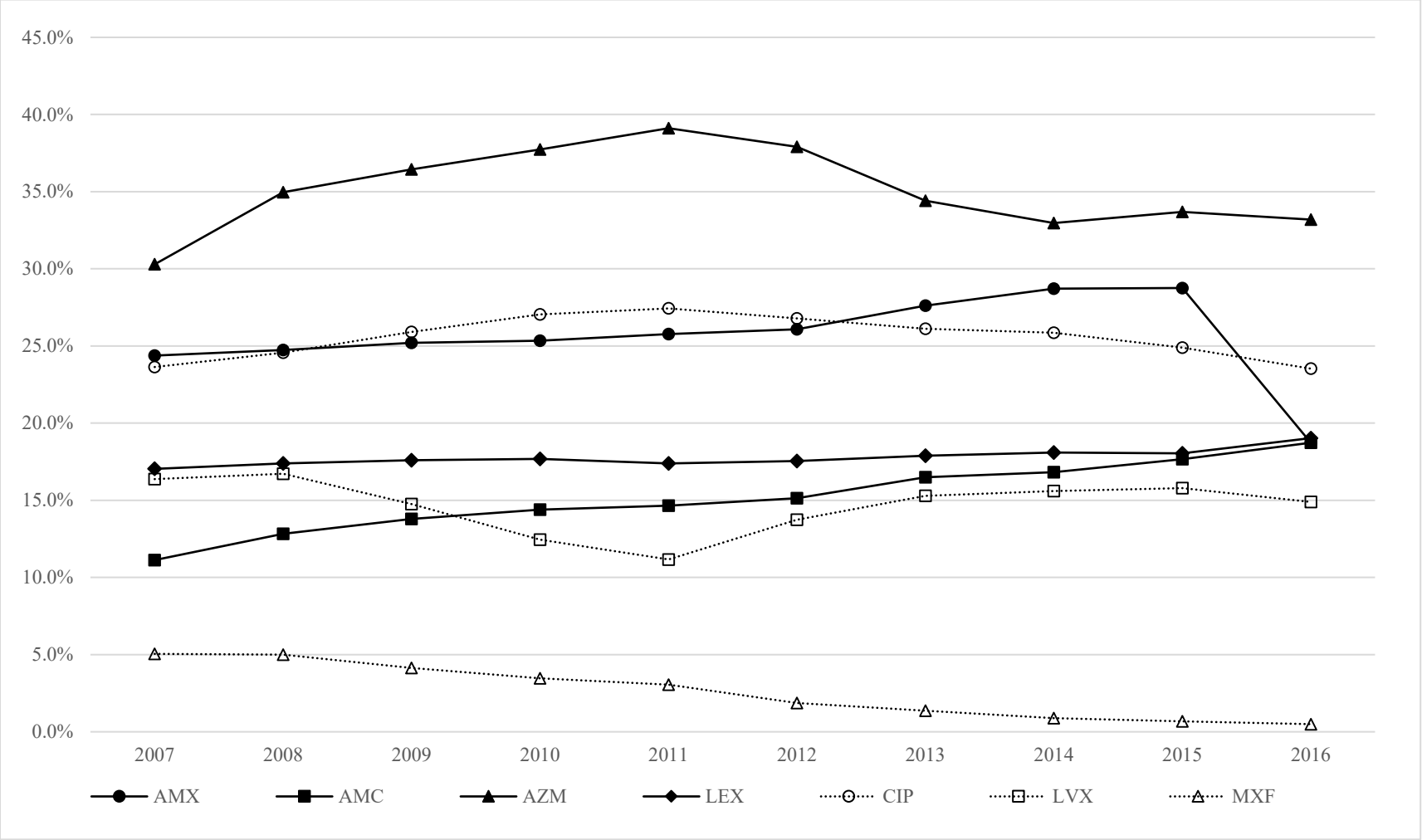
Abbreviations: HR, hazard ratio, CI, confidence interval; FLQ, fluoroquinolone; CIP, ciprofloxacin; LVX, levofloxacin; MXF, moxifloxacin; AMX, Amoxicillin; AMC, Amoxicillin Clavulanate; AZT, Azithromycin; LEX, Cephalexin.

‡ = P-value < 0.001

†= 0.001 ≤ P-value < 0.05



Supplementary Figure. Secular Trend of Study Antibiotic Use



X-axis: Calendar year.

Y-axis: % of patients on each drug class.

STROBE Statement—Checklist of items that should be included in reports of ***case-control studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	6
		(*b*) For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	8-9
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-9
		(*b*) Describe any methods used to examine subgroups and interactions	n/a
		(*c*) Explain how missing data were addressed	n/a
		(*d*) If applicable, explain how matching of cases and controls was addressed	n/a
		(*e*) Describe any sensitivity analyses	n/a
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	9
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9-10
		(b) Indicate number of participants with missing data for each variable of interest	n/a
Outcome data	15*	Report numbers in each exposure category, or summary measures of exposure	10

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-14
		(*b*) Report category boundaries when continuous variables were categorized	12-13
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14-17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

*Give information separately for cases and controls.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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The association between Tendon Ruptures and Use of Fluoroquinolone, and other oral antibiotics: A 10-year Retrospective Study of 1 million U.S. senior Medicare beneficiaries

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3957 Words (4000 MAX)

Abstract (Max 300 words, 286 now)

Objectives: To assess the association of fluoroquinolone use with tendon ruptures compared to no fluoroquinolone and that of the four most commonly prescribed non-fluoroquinolone antibiotics in the US.

Design: Retrospective observational study.

Setting: U.S. senior enrolled in the federal old-age, survivor's insurance program.

Participants: 1,009,925 Medicare fee-for-service beneficiaries and their inpatient, outpatient, prescription drug records were used.

Interventions: Seven oral antibiotics, fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin) and amoxicillin, amoxicillin-clavulanate, azithromycin and cephalexin.

Primary and Secondary Outcome measures: All tendon ruptures combined, and three types of tendon ruptures by anatomic site, Achilles tendon rupture, rupture of rotator cuff and tendon ruptures on other anatomic sites.

Results: Of three fluoroquinolones, only levofloxacin exhibited a significant increased risk of tendon ruptures - 16%, and 120% for rotator cuff and Achilles tendon rupture respectively in the ≤30 day window. Ciprofloxacin and moxifloxacin exhibited little to no increased risk of tendon ruptures. Notably, the risk of levofloxacin never exceeded the risk of the non-fluoroquinolone, cephalexin in any comparison.

Among the non-fluoroquinolone antibiotics, amoxicillin, amoxicillin-clavulanate, and azithromycin exhibited none to benign risk of tendon rupture. Cephalexin exhibited modest to large *increased* risk of tendon rupture at ≤30 day window across all anatomic rupture sites.

Conclusions: In our study, fluoroquinolones as a class were not associated with the increased risk of tendon ruptures. Neither ciprofloxacin nor moxifloxacin exhibited any risk for tendon ruptures. Levofloxacin did exhibit significant increased risk. Cephalexin with no reported effect on metalloprotease activity had an equal or greater risk than levofloxacin; so we question whether metalloprotease activity has any relevance to observed associations with tendon rupture. Confounding by indication bias may be more relevant and should be given more consideration as explanation for significant associations in observational studies of tendon rupture.

Strengths and limitations of this study

- We conducted a large (more than 1 million US senior subjects) retrospective study of outpatient prescription drug records to assess the association between the use of fluoroquinolones and the occurrence of tendon ruptures compared to the most commonly used non-fluoroquinolone oral antibiotics.
- Our study included all oral fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin) prescribed in the US and the four most commonly prescribed non-fluoroquinolone antibiotics: amoxicillin, amoxicillin-clavulanate, azithromycin and cephalexin as controls.
- In addition to reporting the risk of any tendon rupture, we also reported the risk of three types of tendon ruptures by anatomic site 1) Achilles tendon rupture, 2) rupture of rotator cuff and 3) tendon ruptures on other anatomic sites as separate outcomes.
- This study is possibly only applicable to U.S. senior, aged 65 or more, Medicare fee-for-service beneficiaries.
- We had no options to verify claims diagnoses via chart review.

Introduction

Fluoroquinolones (FQ) are among the most widely prescribed antibiotics in the outpatient setting[1,2] due to their broad spectrum treatment of bacteria found in respiratory, urinary, joint, and skin infections. Several observational studies have reported the association between the use of FQs and tendinitis and tendon rupture (TR), especially of the Achilles tendon[3–12] and the U.S. Food and Drug Administration (FDA) issued black box warnings to FQ antibiotics beginning in 2008.[13] The warning was updated in 2016 to recommend using alternative antibiotics when possible.[14,15] The fact that FQs upregulate the production of metalloproteinase enzymes with collagenase activity that could weaken tendons is taken as a mechanism to explain this reported risk.[16–18]

Studies that reported association between FQ use and TR used one or more other antibiotics as controls. One study compared the FQ rupture rates with patients using azithromycin, the most frequently used oral antibiotic in the US. Only two focused principally on TR risk among the elderly. None compared TR rates of *FQs* with those of cephalexin -- the 3rd most commonly prescribed oral antibiotic in the US.

The Virtual Research Data Center (VRDC) of Center for Medicare and Medicaid Services (CMS)[19] carries more than 10 years of Medicare claims, which include information about the usage of prescription drugs and encounter diagnoses (including tendon ruptures). It also carries information about 42 major chronic conditions, demographic characteristic and vital status. We conducted a large observational study using the VRDC to assess the association of FQ antibiotics with TR compared to that of

the four most commonly prescribed non-FQ antibiotics in the US. Here we report the results of that analysis.

Methods

Patient and public involvement

Neither patients nor the public were not involved in the design of the study.

Study population

We derived our study population from a 20% random sample of Medicare prescription drug coverage (Part D) enrollees who first enrolled in the Medicare under old age and survivors insurance within a month of age 65 (779-781 month-old) and on or after 1/1/2007 - the first full year of Part D prescriptions availability. We included claim data through 12/31/2016, the end of VRDC claim data available to us. All of the VRDC data is de-identified and researchers must perform all of their analysis within the VRDC computer systems, and can only pull statistical results from it.[19] We obtained approvals for these studies from the Office of Human Research Protection at the National Institutes of Health as not human subject studies.

We required subjects to be continuously enrolled in hospital insurance (Part A) and medical insurance (Part B) to assure we had full outpatient and inpatient claims data, which are not available for nearly 20% of subjects with Part D only.[20] To obtain a cohort of new TR patients, we excluded individuals with TRs recorded in the first year of their Medicare entitlement.[21] In order to assure sufficient follow-up, we excluded

individuals with less than 1-year follow-up. Moreover, to obtain incident (or new) drug user cohort, we excluded individuals who were prescribed any study antibiotics during their first 3-month after Part D enrollment, while ignoring the data during the same time window for individuals not taking study antibiotics. By doing so, we minimize survivor bias from a prevalent users (Figure 1 Consort Diagram).

Primary Outcome

We identified patients with TR based upon International Classification of Diseases (ICD)-9-CM codes of 726.13, 727.60-727.69, and ICD-10-CM codes of M66.2, M66.3, M66.8, M66.9, and M75.1. We combined all TRs and reported them as one outcome, and report three types of TRs by anatomic site 1) Achilles tendon rupture, 2) rupture of rotator cuff and 3) TRs on other anatomic sites as separate outcomes. We focused on Achilles TR because it was the sole focus of many prior studies and on rotator cuff TR because it is the predominant TR of the elderly. We lumped the remaining as "other TRs".

Study antibiotics

We included a total of seven study antibiotics prescribed in the US including all three oral FQs (moxifloxacin (MXF), ciprofloxacin (CIP), levofloxacin (LVX), the active stereoisomer of ofloxacin) and the four most frequently prescribed non-FQ oral antibiotics (amoxicillin (AMX), amoxicillin clavulanate (AMC), azithromycin (AZT) and cephalexin (LEX)) as a control. Ciprofloxacin and the four non-FQ, study antibiotics were the five most frequently used U.S. oral antibiotics in 2011.

Statistical Analysis

We analyzed each of the four TR outcomes in separate Fine-Gray competing risk regression analyses with death as the competing risk.[22,23] Individuals became eligible for "the study" at their Medicare enrollment but prescription data did not become available until their Part D enrollment. We followed them from their entry in Part D (while accounting for left truncation[24]) until their first diagnosis of TR, death, switch to a capitated plan, disenrollment from Medicare or 12/31/2016 – whichever came first. In each regression analysis, we included the seven antibiotics whose effects on TR were our primary interest. We adjusted hazard ratio (HR) of each study antibiotic for concurrent use of the other study antibiotics. We also adjusted for calendar year of individual's Part D entry, to account for secular trends, and their socio-demographic characteristics of gender, race, rural residency (Yes/No) and income status. We inferred individual's income level from the monthly indicators of dual-eligibility and Low Income Subsidy (LIS) status, which separate subjects into three groups; 1) dual whose income is below 135% Federal Poverty Line (FPL); 2) non-dual LIS whose income is between 135 and 150% FPL; and 3) non-dual no LIS whose income is above 150% FPL, respectively. We used this variable in the analysis as a surrogate for economic status.[25] We also included the 42 chronic conditions within the Medicare Master Beneficiary Summary File [26] that had >1% prevalence as measures of overall health. We assumed that patients were on a given study drug from the prescription dispensing date to the end of days of supply. We did not distinguish between different brands of a study drugs. Following the approach of prior studies,[3–5] we separated subjects by temporal exposure within each study drug,

including groups for never exposed, exposed within 30 days, 31-60 days, and >60 days of the index (or TR event) time. Thus, by this approach we could detect the presumed short term action of the FQ's on tendons and avoid the risk of non-differential misclassification that can occur with too simple (yes/no) drug exposure measures.[27] In order to minimize the immortal time bias, we treated all drug usage measures and all socio-demographic characteristics, except gender, race and rural residency, as time-varying covariates.[28,29] In order to mitigate selection bias toward use of any study antibiotics, we employed a propensity score (PS) approach.[30,31] We first derived a PS of taking any of study antibiotics as a function of individual's characteristics at the time of the first antibiotic use after Part D entry from a multiple logistic regression. We used the median days to the first study antibiotic use in patients taking study antibiotics as the cutoff time for individuals not taking study antibiotics. We performed our analyses with an inverse propensity score weight (IPSW) excluding individuals with the PS below 0.1 and above 0.9, to mitigate poorer performance in the presence of a strong treatment-selection process.[32] In post-hoc analyses, we also compared the risk of TR of each study antibiotics to that of every other study antibiotic on a pairwise basis.

Results

Study population and Secular trend

From our 20% sample of Part D enrollees, 1,009,925 individuals satisfied all our selection criteria including the washout of individuals with any antibiotic use in their first 3-month of Part D enrollment (Figure 1 Consort Diagram). Follow-up began with an individual's enrollment in Part D program (median (IQR) 0 (0-122) days from the

Medicare entitlement). We followed them for a median of 3.6 years (total 4,030,897 patient-years) until their first diagnosis of TR (3.5%), death (4.6%), switch to a capitated plan (12.6%), disenrollment from Medicare (<1%) or study end on 12/31/2016 (79.3%), whichever came first. Patients had their first post enrollment claim with a diagnosis of TR at a median age of 68.5 (IQR 67.2-70.4). The proportions of non-Hispanic White, female and rural residents were 80.7%, 57.0%, and 22.6% respectively. About a fifth of individuals received federal/state subsidies, i.e. Medicaid coverage on top of Medicare (dual 16.1%) or assistance in paying their Part D premium and coinsurance/copayment (non-dual LIS 2.7%). Among the 42 Medicare chronic conditions, hypertension (67.3%), hyperlipidemia (68.4%), cataract (46.4%), rheumatoid arthritis/osteoarthritis (36.6%), anemia (30.4%), ischemic heart disease (26.2%), and chronic kidney disease (17.9%) were the seven most prevalent (Table 1).

Of the 328,654 (33.0%) patients who ever took an FQ, 71.5%, 47.5% and 4.5% had taken CIP, LVX and MXF respectively. Of 576,885 (57.1%) of patients who ever took a non-FQ antibiotic, the figures were 53.6%, 44.9%, 33.9% and 31.1% for AZM, AMX, LEX, and AMC, respectively. Patients who took one or more study antibiotics took a median (IQR) of 3.0 (1.0-6.0) study antibiotic prescriptions and took a median (IQR) 2.0 (1.0-3.0) different study antibiotics during the observation period. About 2.5% patients who took one or more study antibiotics took one or more such antibiotics at the same time. Secular trends in study antibiotics usage existed. MXF usage declined precipitously from 5.0% in 2007 to almost zero in 2016 – overweighting the MXF statistics for early entrants into Medicare and yielding a longer mean follow-up time. CIP use hit a peak, and LVX, a

nadir, in 2011. The use of AMX, AMC and LEX trended slowly upward (Supplementary Figure 1). The mode (median) of supply durations for each antibiotics were short--10 (7) for AMX, 10 (10) for AMC, 5 (5) for AZM, 10 (7) for LEX, 7 (7) for CIP, 10 (7) for LVX, 10 (11) for MXF. About 35% of individuals were never exposed to any of the study antibiotics during the study period.

Unadjusted figures for TR prevalence across each of the seven study antibiotic users and the no study antibiotic users ranged from a high of 5.2% for MXF to a low of 2.9% for no antibiotic (Table 1). Except for MXF, the *unadjusted* prevalence of TRs associated with each non-FQ antibiotic was *greater than* or equal to that of each FQ antibiotic. The TR rates per 1000 patient-years followed the same pattern, with the non-FQ antibiotics topping the rates of all FQs except MXF (with the highest rate), possibly due to overweighting of MXF usage in the early years of the study. Patients who ever took an FQ had the highest unadjusted rate of death per 1000 person-years. LVX's death rate was nearly twice the rate of each non-FQ antibiotics. The size of the associations with conditions like diabetes, chronic renal failure and heart failure paralleled the magnitude of the death rates and was generally higher with FQs than non-FQ antibiotics (Table 1).

Primary Analysis

Table 2 presents HRs for all non-antibiotic covariates in our Fine-Gray competing risk regression with IPSW. For simplicity sake, in Table 2, we report the HRs of all anatomic types of tendon ruptures taken together. Being a female (vs. male), African-American, Hispanic, and Asian (vs. white), being dual or non-dual LIS (vs. non-dual no LIS) and

living in a rural area were all associated with a *reduced* risk of tendon rupture. These risk reductions were 24% or more for all but Hispanics and rural residency covariates, and the reductions were similar across all anatomic sites. In general, life-threatening chronic conditions, such as AMI, COPD, heart failure and colorectal/lung/endometrial cancers were associated with a lower risk of TR in a range of 15-60% below control possibly due to constrained physical activity and/or shortened life span. Notably, diabetes and chronic renal disease, previously reported as risk factors for TR,[33,34] exhibited no increased TR risk. Mobility impairments had reduced risk of TR similar to that of the severe life-threatening conditions, likely due to reduced activity. Most conditions with low life threats such as cataract, glaucoma, depression, asthma, hyperlipidemia, hypertension, prostatic hyperplasia, migraine/other chronic headache, and deafness/hearing impairment exhibited risks of 8 to 34% *above* controls probably for reasons related to longer life spans and less inhibited activity. Ischemic heart did not fit the mold of sicker equals lower TR risk. Patients with rheumatoid arthritis/osteoarthritis were a special case and had TR risk of 184% *above* control possibly due to joint and associated tendon inflammation with these disorders. Fibromyalgia/chronic pain and fatigue also exhibited a 39% increased risk of TR possibly also due to an inflammatory component.

The Achilles tendon carries the full force of the extra weight carried by obese patients and obesity was associated with a significant (13%) increase in Achilles TR ruptures while its effect on other TR classes was significant but miniscule (2-3%) (Data not shown).

Effect of antibiotics

We report HRs from our primary analysis in tables separate from the non-antibiotic covariates. Table 3 shows the risk associated with each study antibiotic broken down by time lag between the antibiotic use and the TRs (separate rows), and by all TRs together and separately by anatomic sites (in columns). We also report HRs of death (competing risk). We used multiplicity corrected p-values to simultaneously test the difference of pairs of antibiotics to minimize the chance of finding statistically significant difference by random chance.[35] Of the total 34,880 patients with any TR occurrence, complete rupture of rotator cuff represented the major share (80.5%), followed by other TRs (16.9%) and Achilles TR (2.6%). In the survival analysis, we followed patients until the first occurrence of TR; so, these figures count only the first TR occurrence independent of anatomic site.

Of the non-FQ antibiotics, AMX exhibited a reduced risk of TR compared to no AMX in every tendon class and time window, similar to its low risk in previous studies. It exhibited a significantly lower risk in the ≤30-day window except for the Achilles tendon. AZM and AMC exhibited a similar benign risk in all time windows except for TR of rotator cuff in >60-day window. LEX was the surprise non-FQ antibiotic. It exhibited modest to large *increase*d TR risk at ≤30-day window across all sites ranging from a low of 19% increase for complete rupture of rotator cuff to a high 93% increase for Achilles TR. Its risk was also significantly higher at ≤30-day window for all TRs taken together.

Of the FQs, CIP and MXF, the most and least frequently prescribed FQ, exhibited little to no increased risk of TR within each anatomic site and each time frame. LVX is the only FQ to exhibit a significant *increase* in TR risk - of 16%, and 120% for rupture of rotator

cuff and Achilles TR respectively in the ≤30-day window. Notably, the risk of LVX never exceeded the risk of the non-FQ, LEX in any comparison.

In a post-hoc analysis (Table 4), we compared the TR risk of each antibiotic with every other antibiotic (pairwise comparisons of FQ vs. FQ and FQ vs. non-FQ), for ≤30-day window and FQs as a class vs. each non-FQ after combining the data from the three time windows. These results paralleled the above-mentioned risk for each study antibiotic in Table 3. Again, TR risk for LVX was greater than that of CIP, MXF, AMC, AMX, and AZM in a ≤30-day window. However, LVX risk was comparable to that of LEX for Achilles TR, and rupture of rotator cuff and significantly lower than LEX for the other TR classes. When comparing the risk of FQs as a class against that of non-FQ antibiotics, most of the non-FQ antibiotics had significantly greater risk than the FQ class as a whole across all TR sites (See last 4 rows of Table 4).

In another analysis evaluating risk of death for each antibiotics, each FQ antibiotic exhibited a significant increase in death risk of – 46% (for CIP), 105% (for MXF) and 119% (for LVX) in a ≤30-day window. Among non-FQ antibiotics, only AMC exhibited 37% increased risk of death in a ≤30-day window. Overall, risk of death for FQs as a class far outweighed that of each non-FQ antibiotics.

Discussion

Our results conflict with the common assertion that the Achilles tendon rupture is the most common tendon rupture (up to 90% in one report[36]). In our elderly cohort, Achilles TRs were a tiny, 2.6%, of all TRs. Some of this difference may be explained by

the differences in demographics. Reports of high prevalence of Achilles TR came from studies of young military populations.[37,38] In contrast, our data came from an elderly Medicare population. Some of the difference could also be due to less ability to diagnose non-Achilles tendon ruptures until MRI joint imaging became widely available, because such TRs are less amenable to diagnosis by physical exam.

Many authorities describe the relationship between FQs and TRs as a class "effect". However, FQs as a class had no significant risk of TR compared with each of the four non-FQ antibiotics in any time window. CIP (n=234,994 subjects) is the oral FQ with the greatest use and with a greater effect on metalloproteases than other FQs.[39–41] However, neither MXF (n= 14,728 subjects) nor CIP had any TR risk at any anatomic site in any time window. CIP's lack of risk is consistent with two studies[5,9] in which CIP exhibited zero risk or small risks compared to ofloxacin, a racemic mixture whose active ingredient is the levo-isomer, LVX. We do see a strong association between LVX and TRs whether we used no LVX or three of the non-FQ antibiotics as controls. However, when we used LEX, a cephalosporin, as the control for LVX's effect on TRs, we saw no increased risk.

As noted in the introduction, the FDA has added a black box warning about tendon ruptures to the labels of fluoroquinolones. A 2015 paper[42] described the evidence for this decision based on the FDA's Adverse Event Reporting System (FAERS) database and an empirical Bayes geometric mean (EBGM) score, which is based on the relative frequency of spontaneous report about a given adverse event in one drug versus the

reporting of that adverse event across all drugs. This EBGM score based upon FAERS database has been useful but FAERS database is still limited by a lack of true denominator for population at risk, underreporting due to a voluntary reporting scheme and bias due to limited adjustment variables.[43] Our study was based on a well-defined Medicare population with 80 variable adjustments. The fact that levofloxacin's EBGM score was six times that of ofloxacin[42] though both drugs have the same active ingredient (the levo-isomer of ofloxacin) and the same dose of that ingredient, raises questions about what factors influenced that score.

One previous study described the effect of FQs on TR risk as small and unimportant.[10] Two studies reported no effect of FQs on TR risk.[9,11] At least 7 observational studies reported that the use of FQs increased risks of TR.[3–8,12] However, in all but one study, the number of TRs among patients taking an FQs was small (between 5 and 111). In comparison, our study included 12,517 (3.8%) such patients. One previous study did report a large number of TR events, 23,000 (3.5%) patients while on FQs and, like our study, it focused exclusively on elderly patients.[3] However, it did not compare the population of FQ users against non-users but FQ usage periods against non-usage periods in the same set of patients, which were likely periods without visits and thus could not account for the effect of increased clinical attention provided at visits requiring a strong systemic antibiotic. Furthermore, they assessed the association between AMX and TRs in separate analysis and used the risk of TRs in that analysis as the comparator for the risk observed in the FQ analysis. Finally, their analysis did not include death as a competing

risk as is recommend when death rates exceed event rates[23] which was likely the case because in the demographics of their study was very similar to ours.

In our study, AMX treated patients had fewer comorbidities (as was also true in Daneman's study), almost 14% fewer hospitalizations and half of death rate per 1000 patient-years, compared to patients taking LVX. So the two populations are not comparable. LVX exhibited 119% increased risk of death in a ≤30-day window. They appears to be reserved for more severe infections or more fragile patients and thus subject to differential biases.

The reported activation of metalloprotease activity by FQs has underpinned the idea of a causal link between FQs and TRs. The argument goes as follows: FQs stimulate metalloproteases, which can break down collagen; the tendon is made of collagen; so FQs may cause TRs. However, our data disrupts this argument. CIP which strongly *stimulates* metalloprotease activity,[17,18] exhibited *no* risk of TRs in our study, and LEX which *inhibits* metalloprotease activity[44,45] exhibited a *large* risk. So we have to question whether metalloprotease activity has any relevance to TR risk, and consider other explanations for the observed associations.

The indication for an antibiotic is a presumed bacterial infection. The reported associations between antibiotics and TR could be a consequence of the indication rather than the antibiotic use and a perfect example of the confounding by indication.[46] Such

a bias could explain many reported associations between drugs and TR risk including associations with non-antibiotic drugs reported by Nyyssönen.[8]

This bias could manifest in different ways. First, that the bacterial infection might directly increase the risk of TR via stimulation of general immune or cytokine responses, or even by direct bacterial invasion. A recent study found gram-positive bacteria in a major share of ruptured tendons but not in "control" tendons removed surgically for grafting,[47] So the possibility of direct invasion of tendons by circulating bacteria with subsequent weakening and rupture is plausible.

Secondly, the greater clinical attention likely focused on patients needing systemic antibiotics, especially those with severe infections, could increase the chance of noticing and documenting a pre-existing TR. A reservoir of not-yet-diagnosed such cases is likely to exist, because patients do not necessarily correctly identify joint and extremity symptoms as TRs and seek immediate care for them. Tendon ruptures of the shoulder capsule, for example, are notorious for developing symptoms slowly over 2-3 years[48] before being correctly diagnosed. Even Achilles tendon ruptures, can be missed (in 30% of cases) at the first presentation.[49] Seeger et al. reviewed the medical records of patients with an insurance claim reporting TRs following antibiotic use and found that nearly half of the TRs recorded in the claims were either something else (e.g., Bursa inflammation miscoded as a TR) or had occurred pre antibiotic use but only seen in a claim post antibiotic use.[11]

Indication bias is a plausible explanations for associations reported in observational studies and it should be considered before assuming the associations are causal.

Limitation

This study faces all of the limitations of observational studies. Furthermore, it applies only to fee-for-service Medicare populations. In addition, we had no options to verify claims diagnoses via chart review. From a statistical point of view, our findings may have some limitations. First, we included 80 covariates in one analysis and concern about possibly strong intercorrelation affecting the validity could exist. To evaluate the intercorrelation among covariates, we calculated an 80x80 correlation matrix of estimated regression coefficients from our competing risk regression analysis considering their time-varying nature. The correlation matrix can deliver information about the strength of all pairwise correlation and indicate the existence of a collinear relationship between two predictors. All correlations (except diagonal elements) were below 0.5, only 1.6% were between 0.2 and 0.5. The largest of the pairwise correlations was 0.33 indicating minimal bias due to intercorrelation. We also did not consider interactions among covariates in our analysis because of the enormous number of two way interactions (as large as 6,400) and thus the problem of overfitting.

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Competing interests Statement

All authors have no competing interest to declare.

Contributorship Statement

SB: study conception, design, analysis and interpretation; critical review of study content; manuscript drafting; approval of the final manuscript. JL: study concept and interpretation; manuscript drafting; approval of the final manuscript. VH: study interpretation; manuscript drafting; approval of the final manuscript. CJM: study conception, design and interpretation; critical review of study content; manuscript drafting; approval of the final manuscript.

Data availability

The authors confirm that the data supporting the findings of this study are available within the article [and/or] its supplementary materials.

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Figure 1. Consort Diagram

Table 1. Outcome, Medical/Medication Use, Diseases and Patient Characteristics by Type of Antibiotics

Variable	Overall	FLQ	CIP	LVX	MXF	AMX	AZM	LEX	AMC	None
N	1,009,925	328,654	234,994	155,991	14,728	259,125	308,985	195,731	179,616	356,364
Tendon Rupture	34,880(3.5)	12,517(3.8)	8,811(3.7)	5,904(3.8)	770(5.2)	9,636(3.7)	12,448(4.0)	8,019(4.1)	6,622(3.7)	10,169(2.9)
Death	46,468(4.6)	23,249(7.1)	14,821(6.3)	14,610(9.4)	2,136(14.5)	9,632(3.7)	14,608(4.7)	11,394(5.8)	9,951(5.5)	13,645(3.8)
Censored at HMO entry	127,162(12.6)	27,573(8.4)	19,847(8.4)	11,142(7.1)	1,571(10.7)	21,215(8.2)	26,140(8.5)	14,887(7.6)	12,674(7.1)	65,886(18.5)
Censored at disenrollment	145(0.0)	25(0.0)	13(0.0)	13(0.0)	2(0.0)	19(0.0)	27(0.0)	23(0.0)	16(0.0)	85(0.0)
Censored at Dec 31 2016	801,270(79.3)	265,290(80.7)	191,502(81.5)	124,322(79.7)	10,249(69.6)	218,623(84.4)	255,762(82.8)	161,408(82.5)	150,353(83.7)	266,579(74.8)
Years of follow-up, median(total)	3.6(4,030,897)	4.6(1,620,894)	4.8(1,190,308)	4.8(789,849)	6.0(87,397)	4.5(1,274,357)	4.6(1,529,370)	4.8(1,000,459)	4.6(890,340)	2.5(1,067,731)
Tendon rupture, 1000 person-years	8.65	7.72	7.40	7.47	8.81	7.56	8.14	8.02	7.44	9.52
Death, 1000 person-years	11.53	14.34	12.45	18.50	24.44	7.56	9.55	11.39	11.18	12.78
Female	575,885(57.0)	197,915(60.2)	146,745(62.4)	89,682(57.5)	8,747(59.4)	151,383(58.4)	194,101(62.8)	113,308(57.9)	104,749(58.3)	191,069(53.6)
White	814,933(80.7)	274,785(83.6)	196,048(83.4)	131,725(84.4)	12,464(84.6)	215,101(83.0)	259,657(84.0)	167,825(85.7)	153,723(85.6)	271,906(76.3)
Black	75,930(7.5)	20,017(6.1)	14,286(6.1)	8,893(5.7)	956(6.5)	15,622(6.0)	17,296(5.6)	9,625(4.9)	9,199(5.1)	35,023(9.8)
Hispanic	56,582(5.6)	17,044(5.2)	12,607(5.4)	7,943(5.1)	628(4.3)	12,494(4.8)	14,805(4.8)	8,976(4.6)	7,802(4.3)	24,391(6.8)
Asian	26,336(2.6)	7,316(2.2)	5,362(2.3)	3,144(2.0)	356(2.4)	7,624(2.9)	7,945(2.6)	3,539(1.8)	3,440(1.9)	10,437(2.9)
Other	36,144(3.6)	9,492(2.9)	6,691(2.8)	4,286(2.7)	324(2.2)	8,284(3.2)	9,282(3.0)	5,766(2.9)	5,452(3.0)	14,607(4.1)
Ever Dual	162,988(16.1)	54,055(16.4)	38,277(16.3)	28,156(18.0)	2,908(19.7)	35,305(13.6)	44,940(14.5)	30,962(15.8)	25,255(14.1)	66,986(18.8)
Non-Dual LIS	26,955(2.7)	7,648(2.3)	5,459(2.3)	3,746(2.4)	385(2.6)	5,224(2.0)	6,828(2.2)	4,191(2.1)	3,818(2.1)	12,595(3.5)
Non-Dual No LIS	819,982(81.2)	266,951(81.2)	191,258(81.4)	124,089(79.5)	11,435(77.6)	218,596(84.4)	257,217(83.2)	160,578(82.0)	150,543(83.8)	276,783(77.7)
Living in rural area	228,199(22.6)	78,581(23.9)	56,385(24.0)	38,847(24.9)	2,801(19.0)	58,805(22.7)	72,282(23.4)	49,977(25.5)	42,288(23.5)	77,087(21.6)
Days on Rx, median (IQR)	N/A	N/A	10.0(7.0-20.0)	10.0(7.0-17.0)	10.0(7.0-12.0)	10.0(7.0-20.0)	5.0(5.0-11.0)	10.0(7.0-16.0)	10.0(10.0-20.0)	N/A
Hospitalization	349,959(29.5)	198,846(45.4)	142,538(45.3)	113,829(52.5)	14,002(60.3)	132,304(38.8)	156,185(37.9)	119,209(45.9)	103,515(42.5)	51,525(14.4)
Outpatient visits per year, median (IQR)	19.6(11.1-33.0)	27.1(17.2-42.7)	27.3(17.5-42.9)	30.1(19.0-47.8)	34.0(21.7-53.7)	23.6(14.5-37.5)	24.6(15.5-38.8)	27.5(17.2-43.2)	26.6(16.7-42.2)	12.3(6.0-21.8)
AMI	21,222(2.1)	9,999(3.0)	6,810(2.9)	5,862(3.8)	698(4.7)	6,474(2.5)	8,079(2.6)	6,215(3.2)	5,292(2.9)	5,012(1.4)
Atrial Fibrillation	71,635(7.1)	31,752(9.7)	21,757(9.3)	17,731(11.4)	2,028(13.8)	23,974(9.3)	26,182(8.5)	21,935(11.2)	18,764(10.4)	16,314(4.6)
Cataract	468,608(46.4)	183,870(55.9)	134,196(57.1)	88,574(56.8)	9,216(62.6)	144,455(55.7)	174,897(56.6)	112,020(57.2)	101,079(56.3)	124,931(35.1)
Chronic Kidney Disease	180,441(17.9)	86,021(26.2)	62,323(26.5)	46,121(29.6)	4,651(31.6)	53,713(20.7)	65,577(21.2)	50,361(25.7)	43,182(24.0)	42,916(12.0)
COPD	130,840(13.0)	71,913(21.9)	43,961(18.7)	48,430(31.0)	6,106(41.5)	40,109(15.5)	66,536(21.5)	37,413(19.1)	37,579(20.9)	22,739(6.4)
Heart Failure	103,010(10.2)	51,814(15.8)	34,870(14.8)	31,377(20.1)	3,776(25.6)	32,792(12.7)	41,647(13.5)	31,585(16.1)	27,223(15.2)	21,907(6.1)
Diabetes	284,919(28.2)	113,424(34.5)	81,175(34.5)	57,697(37.0)	5,942(40.3)	81,155(31.3)	98,176(31.8)	67,548(34.5)	59,984(33.4)	81,448(22.9)
Glaucoma	150,839(14.9)	56,990(17.3)	41,984(17.9)	26,603(17.1)	2,930(19.9)	45,597(17.6)	54,726(17.7)	33,936(17.3)	31,065(17.3)	42,355(11.9)
Hip/Pelvic Fracture	7,982(0.8)	4,086(1.2)	3,000(1.3)	2,289(1.5)	274(1.9)	2,673(1.0)	3,005(1.0)	2,515(1.3)	1,914(1.1)	1,689(0.5)
Ischemic Heart Disease	264,648(26.2)	117,416(35.7)	82,182(35.0)	63,659(40.8)	6,956(47.2)	83,682(32.3)	101,999(33.0)	70,612(36.1)	63,363(35.3)	63,372(17.8)
Depression	210,714(20.9)	94,554(28.8)	68,625(29.2)	49,277(31.6)	5,298(36.0)	65,642(25.3)	83,253(26.9)	56,747(29.0)	51,150(28.5)	49,320(13.8)
Alzheimer's Disease or Senile Dementia	39,132(3.9)	19,796(6.0)	14,309(6.1)	11,030(7.1)	1,206(8.2)	11,140(4.3)	13,809(4.5)	11,846(6.1)	9,309(5.2)	9,400(2.6)
Osteoporosis	106,966(10.6)	47,033(14.3)	35,217(15.0)	22,918(14.7)	2,738(18.6)	34,610(13.4)	44,016(14.2)	26,996(13.8)	24,393(13.6)	25,216(7.1)

Rheumatoid Arthritis/Osteoarthritis	369,584(36.6)	160,091(48.7)	117,018(49.8)	80,115(51.4)	8,259(56.1)	126,702(48.9)	148,653(48.1)	101,310(51.8)	88,017(49.0)	81,855(23.0)
Stroke/Transient Ischemic Attack	58,886(5.8)	27,702(8.4)	19,843(8.4)	15,051(9.6)	1,670(11.3)	17,829(6.9)	22,038(7.1)	16,684(8.5)	14,245(7.9)	14,262(4.0)
Breast Cancer	45,316(4.5)	19,362(5.9)	14,344(6.1)	9,442(6.1)	984(6.7)	13,451(5.2)	17,676(5.7)	12,543(6.4)	10,156(5.7)	11,042(3.1)
Colorectal Cancer	15,905(1.6)	7,487(2.3)	5,421(2.3)	4,048(2.6)	390(2.6)	4,304(1.7)	5,170(1.7)	4,085(2.1)	3,605(2.0)	4,104(1.2)
Prostate Cancer	37,038(3.7)	19,705(6.0)	15,577(6.6)	9,232(5.9)	643(4.4)	10,967(4.2)	11,733(3.8)	9,252(4.7)	8,070(4.5)	8,333(2.3)
Lung Cancer	14,946(1.5)	8,965(2.7)	5,144(2.2)	6,356(4.1)	905(6.1)	3,859(1.5)	6,633(2.1)	3,977(2.0)	4,267(2.4)	2,733(0.8)
Endometrial Cancer	7,396(0.7)	3,447(1.0)	2,670(1.1)	1,635(1.0)	160(1.1)	2,095(0.8)	2,637(0.9)	1,957(1.0)	1,604(0.9)	1,847(0.5)
Anemia	307,310(30.4)	140,606(42.8)	100,819(42.9)	74,308(47.6)	7,980(54.2)	99,190(38.3)	118,327(38.3)	81,967(41.9)	72,587(40.4)	71,098(20.0)
Asthma	86,120(8.5)	46,350(14.1)	29,327(12.5)	30,152(19.3)	4,091(27.8)	27,632(10.7)	46,823(15.2)	24,426(12.5)	25,465(14.2)	13,802(3.9)
Hyperlipidemia	691,148(68.4)	257,086(78.2)	185,199(78.8)	123,828(79.4)	12,162(82.6)	199,236(76.9)	239,414(77.5)	152,879(78.1)	140,364(78.1)	201,258(56.5)
Hyperplasia	122,010(12.1)	59,809(18.2)	45,517(19.4)	28,616(18.3)	2,587(17.6)	39,031(15.1)	42,070(13.6)	31,606(16.1)	28,398(15.8)	27,336(7.7)
Hypertension	679,287(67.3)	253,601(77.2)	181,231(77.1)	124,646(79.9)	12,218(83.0)	192,686(74.4)	230,409(74.6)	150,995(77.1)	136,292(75.9)	201,777(56.6)
Hypothyroidism	197,447(19.6)	81,468(24.8)	59,450(25.3)	40,372(25.9)	4,198(28.5)	59,893(23.1)	76,582(24.8)	47,973(24.5)	44,249(24.6)	50,280(14.1)
Anxiety Disorders	148,983(14.8)	70,688(21.5)	51,377(21.9)	37,563(24.1)	4,032(27.4)	48,859(18.9)	62,418(20.2)	41,655(21.3)	37,588(20.9)	31,709(8.9)
Bipolar Disorder	17,882(1.8)	8,368(2.5)	6,104(2.6)	4,533(2.9)	468(3.2)	5,442(2.1)	6,658(2.2)	5,147(2.6)	4,227(2.4)	4,242(1.2)
Major Depressive Affective Disorder	153,182(15.2)	71,732(21.8)	52,101(22.2)	38,055(24.4)	4,148(28.2)	48,846(18.9)	61,872(20.0)	43,416(22.2)	38,642(21.5)	33,660(9.4)
Schizophrenia and other Psychotic Disorders	16,764(1.7)	8,591(2.6)	6,176(2.6)	4,934(3.2)	548(3.7)	4,421(1.7)	5,597(1.8)	5,101(2.6)	3,811(2.1)	4,300(1.2)
Epilepsy	16,155(1.6)	7,543(2.3)	5,383(2.3)	4,269(2.7)	415(2.8)	4,310(1.7)	5,488(1.8)	4,510(2.3)	3,621(2.0)	4,191(1.2)
Fibromyalgia, Chronic Pain and Fatigue	166,279(16.5)	78,877(24.0)	57,494(24.5)	41,843(26.8)	4,410(29.9)	56,152(21.7)	70,667(22.9)	48,422(24.7)	43,379(24.2)	33,843(9.5)
Viral Hepatitis (General)	11,969(1.2)	4,659(1.4)	3,188(1.4)	2,523(1.6)	287(1.9)	3,156(1.2)	3,732(1.2)	2,712(1.4)	2,348(1.3)	3,735(1.0)
Liver Disease Cirrhosis and other Liver Conditions	62,675(6.2)	31,930(9.7)	23,284(9.9)	17,386(11.1)	1,919(13.0)	19,624(7.6)	24,544(7.9)	17,393(8.9)	15,958(8.9)	13,350(3.7)
Leukemias and Lymphomas	13,906(1.4)	7,228(2.2)	4,822(2.1)	4,536(2.9)	551(3.7)	4,385(1.7)	5,905(1.9)	4,025(2.1)	3,969(2.2)	2,758(0.8)
Migraine and other Chronic Headache	31,628(3.1)	14,936(4.5)	11,282(4.8)	7,520(4.8)	873(5.9)	10,841(4.2)	13,893(4.5)	8,763(4.5)	8,403(4.7)	6,419(1.8)
Mobility Impairments	20,600(2.0)	10,182(3.1)	7,356(3.1)	5,767(3.7)	577(3.9)	5,372(2.1)	6,629(2.1)	5,995(3.1)	4,610(2.6)	5,439(1.5)
Obesity	185,101(18.3)	79,130(24.1)	56,609(24.1)	41,226(26.4)	3,997(27.1)	58,654(22.6)	69,611(22.5)	49,984(25.5)	43,740(24.4)	44,772(12.6)
Peripheral Vascular Disease	90,132(8.9)	45,276(13.8)	31,866(13.6)	25,977(16.7)	3,001(20.4)	28,747(11.1)	36,241(11.7)	28,343(14.5)	23,977(13.3)	18,446(5.2)
Tobacco Use Disorders	101,890(10.1)	45,304(13.8)	28,907(12.3)	27,202(17.4)	3,042(20.7)	27,261(10.5)	37,860(12.3)	25,002(12.8)	22,975(12.8)	26,896(7.5)
Pressure Ulcers and Chronic Ulcers	30,345(3.0)	17,688(5.4)	12,800(5.4)	10,603(6.8)	1,196(8.1)	9,006(3.5)	10,926(3.5)	13,404(6.8)	9,960(5.5)	4,992(1.4)
Deafness and Hearing Impairment	59,576(5.9)	27,383(8.3)	19,976(8.5)	14,014(9.0)	1,609(10.9)	21,213(8.2)	25,498(8.3)	16,849(8.6)	16,787(9.3)	11,900(3.3)

Note. Data are presented as No. (%) of patients unless otherwise noted.
Abbreviations: FLQ, fluoroquinolone; CIP, ciprofloxacin; LVX, levofloxacin; MXF, moxifloxacin; AMX, Amoxicillin; AMC, Amoxicillin Clavulanate; AZT, Azithromycin; LEX, Cephalexin; IQR, interquartile range.

Table 2. Hazard Ratios of Tendon Rupture for Each Covariate

Variables	Reference	HR(95% CI)
Female	Male	0.70(0.69,0.72)↓
Black	White	0.76(0.73,0.78)↓
Hispanic		0.91(0.87,0.94)↓
Asian		0.67(0.63,0.71)↓
Other		1.05(1.01,1.09)↑
Dual Ever	Non-Dual Non-LIS	0.66(0.64,0.68)↓
Non-Dual Lis		0.66(0.63,0.70)↓
Living In Rural Area	No	0.94(0.92,0.95)↓
Medicare Part D Since 2008	Medicare Part D Since 2007	1.03(1.00,1.07)
Medicare Part D Since 2009		1.11(1.07,1.15)↑
Medicare Part D Since 2010		1.16(1.12,1.21)↑
Medicare Part D Since 2011		1.17(1.13,1.22)↑
Medicare Part D Since 2012		1.12(1.08,1.16)↑
Medicare Part D Since 2013		1.03(1.00,1.07)
Medicare Part D Since 2013		1.05(1.01,1.09)↑
Medicare Part D Since 2015		0.91(0.87,0.96)↓
Medicare Part D Since 2016		0.93(0.19,4.55)
AMI	No	0.74(0.69,0.79)↓
Atrial Fibrillation	No	0.94(0.91,0.97)↓
Cataract	No	1.23(1.21,1.25)↑
Chronic Kidney Disease	No	0.92(0.89,0.94)↓
COPD	No	0.83(0.81,0.86)↓
Heart Failure	No	0.79(0.77,0.82)↓
Diabetes	No	0.98(0.96,0.99)↓
Glaucoma	No	1.10(1.08,1.12)↑
Hip/Pelvic Fracture	No	0.68(0.60,0.77)↓
Ischemic Heart Disease	No	1.10(1.08,1.12)↑
Depression	No	1.17(1.13,1.21)
Alzheimer's Disease or Senile Dementia	No	0.67(0.63,0.71)↓
Osteoporosis	No	1.03(1.01,1.06)↑
Rheumatoid Arthritis/Osteoarthritis	No	2.84(2.80,2.89)↑
Stroke/Transient Ischemic Attack	No	0.97(0.94,1.01)
Breast Cancer	No	0.94(0.91,0.98)↓
Colorectal Cancer	No	0.79(0.74,0.85)↓

Prostate Cancer	No	1.03(0.99,1.07)
Lung Cancer	No	0.39(0.34,0.45)↡
Endometrial Cancer	No	0.85(0.77,0.94)↓
Anemia	No	1.01(0.99,1.03)
Asthma	No	1.27(1.24,1.31)↟
Hyperlipidemia	No	1.34(1.31,1.36)↟
Hyperplasia	No	1.13(1.10,1.16)↟
Hypertension	No	1.09(1.07,1.11)↟
Hypothyroidism	No	1.08(1.06,1.10)↟
Anxiety Disorders	No	0.98(0.96,1.01)
Bipolar Disorder	No	1.02(0.95,1.08)
Major Depressive Affective Disorder	No	1.06(1.02,1.10)↑
Schizophrenia and Other Psychotic Disorders	No	0.67(0.61,0.74)↡
Epilepsy	No	0.83(0.77,0.90)↡
Fibromyalgia, Chronic Pain and Fatigue	No	1.39(1.36,1.42)↟
Viral Hepatitis (General)	No	1.04(0.96,1.13)
Liver Disease Cirrhosis And Other Liver Conditions	No	0.95(0.92,0.99)↓
Leukemias and Lymphomas	No	0.94(0.88,1.01)
Migraine and Other Chronic Headache	No	1.28(1.23,1.33)↟
Mobility Impairments	No	0.70(0.65,0.76)↡
Obesity	No	1.04(1.02,1.06)↑
Peripheral Vascular Disease	No	1.00(0.97,1.04)
Tobacco Use Disorders	No	0.82(0.80,0.85)↡
Pressure Ulcers and Chronic Ulcers	No	0.82(0.77,0.87)↡
Deafness and Hearing Impairment	No	1.21(1.17,1.25)↟

Hazard ratios and confidence intervals from the primary analysis for Covariates except for the study antibiotics (which are in Table 3)

Abbreviations: HR, hazard ratio, CI, confidence interval; FLQ, fluoroquinolone; CIP, ciprofloxacin; LVX, levofloxacin; MXF, moxifloxacin; AMX, Amoxicillin; AMC, Amoxicillin Clavulanate; AZT, Azithromycin; LEX, Cephalexin.

↟= significantly high with P-value < 0.001, ↑= significantly high with 0.001 ≤ P-value < 0.05
↡= significantly low with P-value < 0.001, ↓= significantly high with 0.001 ≤ P-value < 0.05

Table 3. Hazard Ratios of Each Antibiotic by Anatomic Sites and Temporal Order of Drug Exposure

		Any Tendon Rupture	Achilles Tendon Rupture	Complete Rupture of Rotator Cuff	Other Tendon Rupture	Death (Competing risk)
	Temporal Exposure	HR(95% CI)	HR(95% CI)	HR(95% CI)	HR(95% CI)	HR(95% CI)
HRs comparing study antibiotic use with no use						
AMX VS. NO AMX	**<= 30**	0.86(0.80,0.92)↓	0.88(0.59,1.33)	0.88(0.82,0.95)↓	0.79(0.67,0.93)↓	0.66(0.61,0.71)↓
	31 - 60	0.94(0.87,1.01)	0.80(0.49,1.31)	0.91(0.84,0.99)↓	1.08(0.93,1.27)	0.69(0.63,0.75)↓
	≥ 61	1.00(0.98,1.02)	0.99(0.86,1.13)	1.01(0.99,1.04)	0.97(0.92,1.01)	0.77(0.75,0.78)↓
AMC VS. NO AMC	**<= 30**	0.93(0.85,1.02)	1.25(0.79,1.97)	0.87(0.79,0.97)↓	1.17(0.98,1.41)	0.80(0.75,0.84)↓
	31 - 60	0.95(0.85,1.05)	1.37(0.82,2.29)	0.95(0.84,1.06)	0.81(0.63,1.04)	0.77(0.73,0.82)↓
	≥ 61	1.07(1.04,1.09)↑	0.95(0.81,1.12)	1.07(1.04,1.10)↑	1.02(0.96,1.08)	0.71(0.70,0.72)↓
AZM VS. NO AZM	**<= 30**	0.99(0.93,1.06)	1.15(0.82,1.63)	1.00(0.93,1.08)	0.87(0.75,1.01)	1.04(0.98,1.10)
	31 - 60	0.90(0.84,0.98)↓	0.99(0.65,1.49)	0.91(0.84,0.99)↓	0.95(0.81,1.11)	1.01(0.94,1.08)
	≥ 61	1.07(1.05,1.09)↑	1.02(0.91,1.15)	1.09(1.07,1.12)↑	0.99(0.95,1.04)	0.86(0.84,0.88)↓
LEX VS. NO LEX	**<= 30**	1.31(1.22,1.41)↑	1.93(1.35,2.75)↑	1.19(1.09,1.29)↑	1.79(1.56,2.06)↑	1.46(1.40,1.53)↑
	31 - 60	1.05(0.95,1.15)	1.14(0.66,1.96)	1.06(0.96,1.18)	1.02(0.82,1.26)	1.31(1.24,1.38)↑
	≥ 61	1.08(1.05,1.11)↑	1.00(0.85,1.16)	1.07(1.05,1.10)↑	1.15(1.09,1.21)↑	0.86(0.84,0.88)↓
LVX VS. NO LVX	**<= 30**	1.14(1.05,1.25)↑	2.20(1.50,3.24)↑	1.16(1.06,1.28)↑	0.96(0.78,1.19)	2.19(2.11,2.28)↑
	31 - 60	1.09(0.98,1.21)	1.91(1.17,3.10)↑	1.09(0.97,1.22)	1.14(0.90,1.43)	1.80(1.71,1.89)↑
	≥ 61	1.02(1.00,1.05)	1.22(1.03,1.43)↑	1.03(1.00,1.07)↑	0.97(0.91,1.03)	0.99(0.97,1.01)
CIP VS. NO CIP	**<= 30**	0.96(0.89,1.03)	1.06(0.70,1.60)	0.96(0.88,1.04)	0.84(0.71,1.00)↓	2.05(1.78,2.35)↑
	31 - 60	0.92(0.85,1.01)	1.02(0.63,1.67)	0.91(0.82,1.00)↓	0.95(0.78,1.14)	1.43(1.18,1.72)↑
	≥ 61	0.96(0.94,0.98)↓	1.16(1.02,1.32)↑	0.96(0.94,0.99)↓	0.92(0.88,0.97)↓	0.89(0.86,0.93)↓
MXF VS. NO MXF	**<= 30**	0.59(0.37,0.93)	0.97(0.15,6.24)	0.52(0.30,0.91)↓	0.76(0.33,1.77)	1.37(1.30,1.45)↑
	31 - 60	0.71(0.43,1.15)	0.00(0.00,0.00)	0.63(0.35,1.13)	0.93(0.39,2.25)	1.26(1.17,1.35)↑
	≥ 61	0.99(0.93,1.06)	1.02(0.69,1.51)	0.99(0.92,1.06)	1.10(0.95,1.27)	0.86(0.84,0.88)↓
HRs comparing use of FQ as a class with use of each non-FQ antibiotics						
FLQ VS. AMX	**<= 30**	1.00(0.84,1.19)	1.49(0.69,3.19)	0.94(0.77,1.16)	1.08(0.77,1.50)	2.86(2.61,3.13)↑
	31 - 60	0.95(0.79,1.15)	0.07(0.04,0.12)↓	0.94(0.75,1.17)	0.92(0.65,1.31)	2.18(1.96,2.44)↑
	≥ 61	0.99(0.96,1.02)	1.14(0.94,1.40)	0.98(0.95,1.02)	1.03(0.96,1.11)	1.19(1.16,1.22)↑
FLQ VS. AZM	**<= 30**	0.87(0.73,1.03)	1.14(0.54,2.39)	0.83(0.68,1.02)	0.98(0.70,1.37)	2.35(2.18,2.53)↑
	31 - 60	0.99(0.82,1.19)	0.06(0.04,0.09)↓	0.93(0.75,1.16)	1.06(0.75,1.49)	1.94(1.77,2.13)↑
	≥ 61	0.93(0.90,0.96)↓	1.10(0.91,1.34)	0.91(0.88,0.94)↓	1.00(0.93,1.08)	1.29(1.25,1.32)↑
FLQ VS. LEX	**<= 30**	0.66(0.55,0.78)↓	0.68(0.32,1.42)	0.70(0.57,0.87)↓	0.47(0.34,0.66)↓	1.80(1.67,1.95)↑
	31 - 60	0.85(0.70,1.04)	0.05(0.03,0.09)↓	0.80(0.64,1.01)	0.99(0.68,1.44)	1.48(1.34,1.64)↑

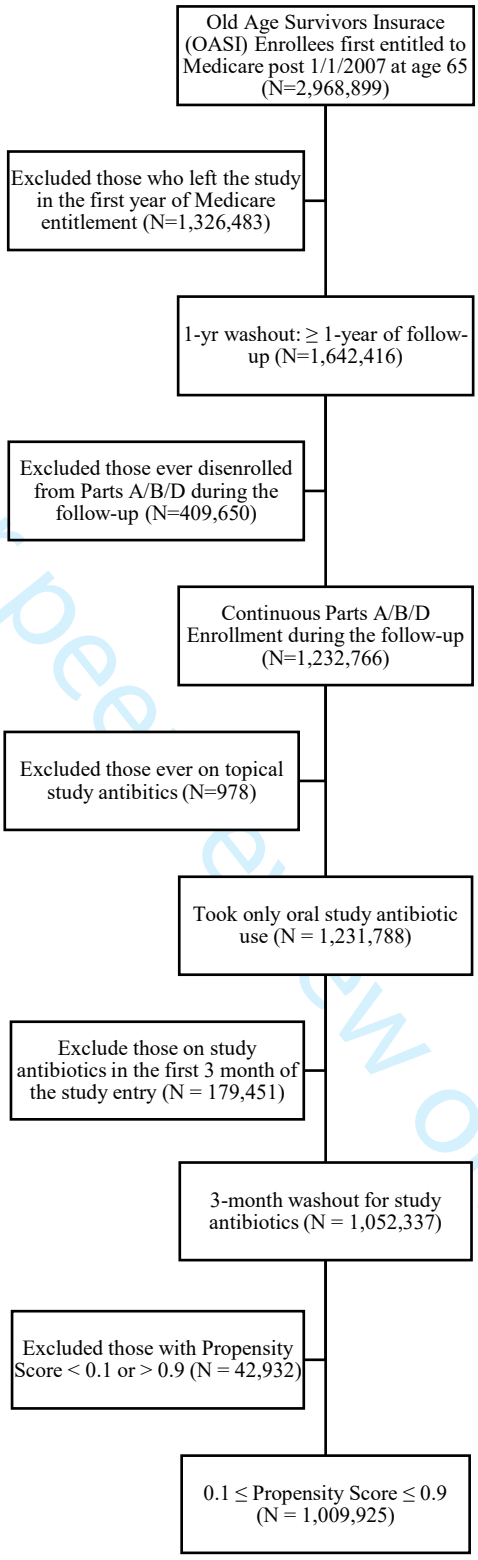
	≥ 61	0.92(0.89,0.95)↓	1.13(0.92,1.40)	0.92(0.89,0.96)↓	0.86(0.80,0.93)↓	1.06(1.03,1.09)↑
FLQ VS. AMC	**<= 30**	0.93(0.77,1.11)	1.05(0.48,2.32)	0.96(0.77,1.19)	0.72(0.51,1.02)	1.37(1.27,1.48)↑
	31 - 60	0.94(0.77,1.15)	0.04(0.02,0.07)↓	0.90(0.72,1.14)	1.24(0.83,1.86)	1.19(1.08,1.31)↑
	≥ 61	0.93(0.90,0.97)↓	1.19(0.95,1.49)	0.93(0.89,0.96)↓	0.98(0.90,1.06)	1.06(1.03,1.09)↑

Abbreviations: HR, hazard ratio, CI, confidence interval; FLQ, fluoroquinolone; CIP, ciprofloxacin; LVX, levofloxacin; MXF, moxifloxacin; AMX, Amoxicillin; AMC, Amoxicillin Clavulanate; AZT, Azithromycin; LEX, Cephalexin.
↑= significantly high with P-value < 0.001, ↑= significantly high with 0.001 ≤ P-value < 0.05
↓= significantly low with P-value < 0.001, ↓= significantly high with 0.001 ≤ P-value < 0.05

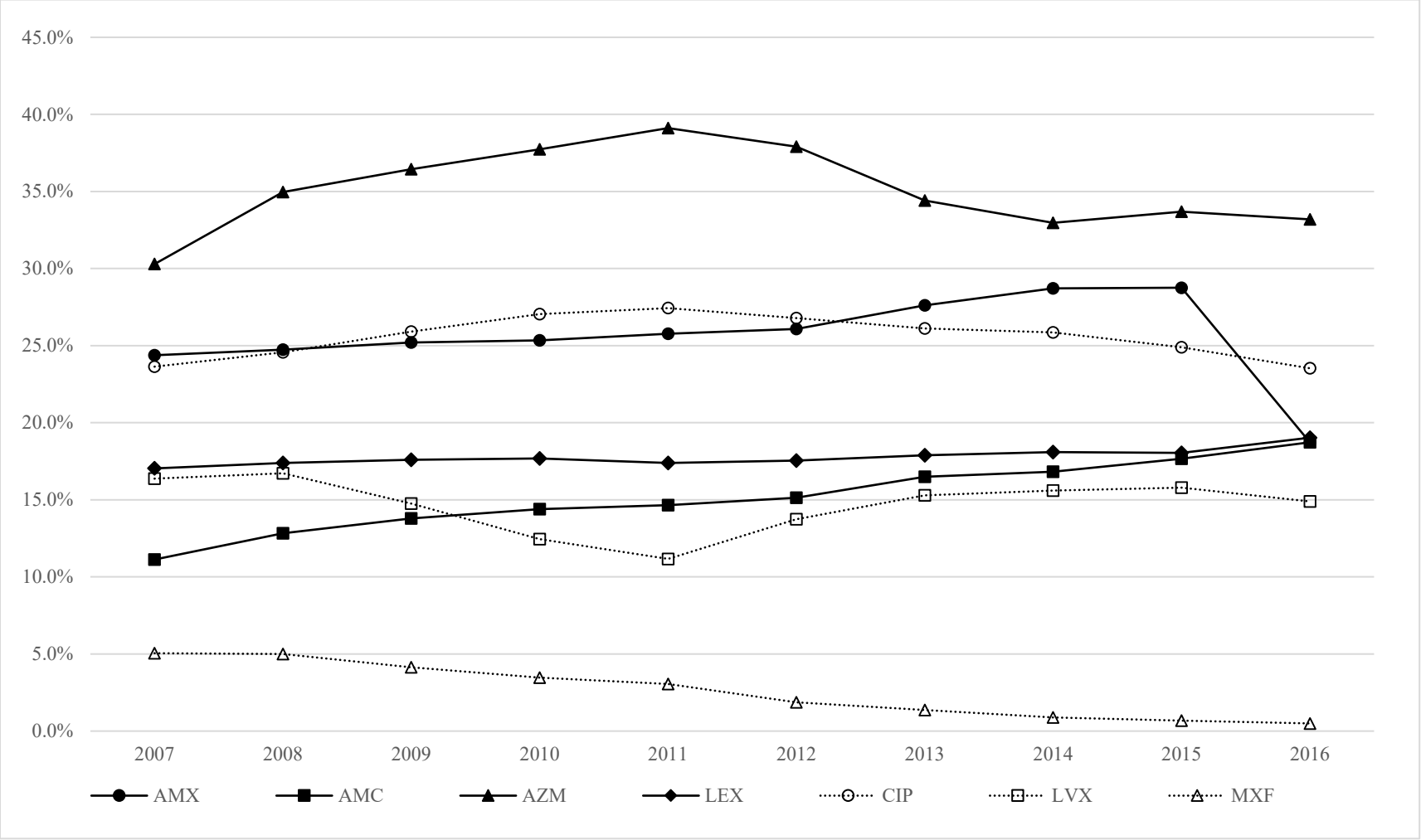
Table 4. Pairwise Comparisons

Comparison	Temporal Exposure	Any Tendon Rupture HR(95% CI)	Achilles Tendon Rupture HR(95% CI)	Complete Rupture of Rotator Cuff HR(95% CI)	Other Tendon Rupture HR(95% CI)	Death (Competing risk) HR(95% CI)
HRs comparing use of each FQ with use of each non-FQ antibiotics in a ≤30-day window						
CIP VS. LVX	**<= 30**	0.84(0.75,0.94)↓	0.48(0.27,0.86) ↓	0.82(0.73,0.94) ↓	0.87(0.67,1.15)	0.67(0.63,0.71)↓↓
CIP VS. MXF	**<= 30**	1.63(1.02,2.61)↑	1.08(0.16,7.29)	1.84(1.05,3.24)↑	1.10(0.47,2.60)	0.72(0.62,0.83)↓↓
LVX VS. MXF	**<= 30**	1.95(1.21,3.13)↑	2.26(0.34,15.17)	2.24(1.27,3.94)↑	1.26(0.53,3.01)	1.07(0.93,1.24)
CIP VS. AMX	**<= 30**	1.11(1.01,1.23)↑	1.20(0.66,2.16)	1.09(0.97,1.21)	1.06(0.84,1.34)	2.23(2.05,2.44)↑↑
CIP VS. AZM	**<= 30**	0.97(0.87,1.06)	0.91(0.53,1.57)	0.96(0.86,1.07)	0.96(0.77,1.21)	1.84(1.71,1.97)↑↑
CIP VS. LEX	**<= 30**	0.73(0.66,0.81)↓↓	0.55(0.31,0.95) ↓	0.81(0.72,0.91)↓↓	0.47(0.37,0.59)↑↑	1.41(1.31,1.52)↑↑
CIP VS. AMC	**<= 30**	1.03(0.91,1.16)	0.84(0.46,1.56)	1.10(0.96,1.25)	0.71(0.56,0.92)↓	1.07(1.00,1.15)
LVX VS. AMX	**<= 30**	1.33(1.19,1.49)↑↑	2.50(1.45,4.29)↑	1.32(1.16,1.49)↑↑	1.22(0.93,1.59)	3.34(3.07,3.64)↑↑
LVX VS. AZM	**<= 30**	1.15(1.03,1.29)↑	1.91(1.13,3.23)↑	1.16(1.03,1.31)↑	1.10(0.84,1.44)	2.75(2.57,2.95)↑↑
LVX VS. LEX	**<= 30**	0.87(0.78,0.98) ↓	1.14(0.68,1.92)	0.98(0.86,1.12)	0.54(0.41,0.69)↑↑	2.11(1.97,2.27)↑↑
LVX VS. AMC	**<= 30**	1.23(1.08,1.40)↑	1.76(0.98,3.15)	1.33(1.15,1.54)↑↑	0.82(0.62,1.08)	1.60(1.49,1.72)↑↑
MXF VS. AMX	**<= 30**	0.68(0.43,1.09)	1.10(0.16,7.41)	0.59(0.34,1.03)	0.96(0.41,2.27)	3.12(2.67,3.65)↑↑
MXF VS. AZM	**<= 30**	0.59(0.37,0.94) ↓	0.84(0.13,5.65)	0.52(0.30,0.91)↓	0.88(0.37,2.07)	2.57(2.21,2.98)↑↑
MXF VS. LEX	**<= 30**	0.45(0.28,0.72) ↓	0.50(0.08,3.35)	0.44(0.25,0.77)↓	0.43(0.18,1.00)	1.97(1.70,2.‡29)↑↑
MXF VS. AMC	**<= 30**	0.63(0.39,1.01)	0.78(0.11,5.33)	0.60(0.34,1.05)	0.65(0.28,1.53)	1.50(1.29,1.73)↑↑
HRs comparing use of FQ as a class with use of each non-FQ antibiotics across different time window						
FLQ VS. AMX	**Overall**	0.98(0.90,1.07)	0.49(0.36,0.68)	0.95(0.86,1.06)	1.01(0.86,1.19)	1.95(1.86,2.05)↑↑
FLQ VS. AZM	**Overall**	0.93(0.85,1.01)	0.42(0.30,0.57)	0.89(0.80,0.98)↓	1.01(0.86,1.19)	1.80(1.73,1.88)↑↑
FLQ VS. LEX	**Overall**	0.80(0.73,0.88)	0.34(0.24,0.47)	0.80(0.72,0.89)	0.74(0.62,0.88)	1.42(1.35,1.48)↑↑
FLQ VS. AMC	**Overall**	0.93(0.85,1.02)	0.37(0.26,0.52)	0.93(0.83,1.03)	0.96(0.80,1.15)	1.20(1.15,1.25)↑↑

Abbreviations: HR, hazard ratio, CI, confidence interval; FLQ, fluoroquinolone; CIP, ciprofloxacin; LVX, levofloxacin; MXF, moxifloxacin; AMX, Amoxicillin; AMC, Amoxicillin Clavulanate; AZT, Azithromycin; LEX, Cephalexin.
↑↑= significantly high with P-value < 0.001, ↑= significantly high with 0.001 ≤ P-value < 0.05
↓↓= significantly low with P-value < 0.001, ↓= significantly high with 0.001 ≤ P-value < 0.05



Supplementary Figure. Secular Trend of Study Antibiotic Use



X-axis: Calendar year.

Y-axis: % of patients on each drug class.

STROBE Statement—Checklist of items that should be included in reports of ***case-control studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	6
		(*b*) For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	8-9
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-9
		(*b*) Describe any methods used to examine subgroups and interactions	n/a
		(*c*) Explain how missing data were addressed	n/a
		(*d*) If applicable, explain how matching of cases and controls was addressed	n/a
		(*e*) Describe any sensitivity analyses	n/a
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	9
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9-10
		(b) Indicate number of participants with missing data for each variable of interest	n/a
Outcome data	15*	Report numbers in each exposure category, or summary measures of exposure	10

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-14
		(*b*) Report category boundaries when continuous variables were categorized	12-13
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14-17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

*Give information separately for cases and controls.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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The association between Tendon Ruptures and Use of Fluoroquinolone, and other oral antibiotics: A 10-year Retrospective Study of 1 million U.S. senior Medicare beneficiaries

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The association between Tendon Ruptures and Use of Fluoroquinolone, and other oral antibiotics: A 10-year Retrospective Study of 1 million U.S. senior Medicare beneficiaries

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4000 Words (4000 Max)

Abstract (298 words; 300 Max)

Objectives: To assess the association of fluoroquinolone use with tendon ruptures compared to no fluoroquinolone and that of the four most commonly prescribed non-fluoroquinolone antibiotics in the US.

Design: Retrospective observational study.

Setting: U.S. seniors enrolled in the federal old-age, survivor's insurance program.

Participants: 1,009,925 Medicare fee-for-service beneficiaries and their inpatient, outpatient, prescription drug records were used.

Interventions: Seven oral antibiotics, fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin) and amoxicillin, amoxicillin-clavulanate, azithromycin and cephalexin.

Primary and Secondary Outcome measures: All tendon ruptures combined, and three types of tendon ruptures by anatomic site, Achilles tendon rupture, rupture of rotator cuff and other tendon ruptures occurred in 2007-2016.

Results: Of three fluoroquinolones, only levofloxacin exhibited a significant increased risk of tendon ruptures - 16% (HR=1.16; 95% CI 1.06-1.28), and 120% (HR=2.20; 95% CI 1.50-3.24) for rotator cuff and Achilles tendon rupture respectively in the ≤30-day window. Ciprofloxacin (HR=0.96; 95% CI 0.89-1.03) and moxifloxacin (HR=0.59; 95% CI 0.37-0.93) exhibited no increased risk of tendon ruptures combined.

Among the non-fluoroquinolone antibiotics, cephalexin exhibited *increased* risk of combined tendon ruptures (HR=1.31; 95% CI 1.22-1.41) and modest to large risks across all anatomic rupture sites (HRs 1.19-1.93) at ≤30-day window. Notably, the risk of

levofloxacin never exceeded the risk of the non-fluoroquinolone, cephalexin in any comparison.

Conclusions: In our study, fluoroquinolones as a class were not associated with the increased risk of tendon ruptures. Neither ciprofloxacin nor moxifloxacin exhibited any risk for tendon ruptures. Levofloxacin did exhibit significant increased risk. Cephalexin with no reported effect on metalloprotease activity had an equal or greater risk than levofloxacin; so we question whether metalloprotease activity has any relevance to observed associations with tendon rupture. Confounding by indication bias may be more relevant and should be given more consideration as explanation for significant associations in observational studies of tendon rupture.

Strengths and limitations of this study

- We conducted a large (more than 1 million US senior subjects) retrospective study of outpatient prescription drug records to assess the association between the use of fluoroquinolones and the occurrence of tendon ruptures compared to the most commonly used non-fluoroquinolone oral antibiotics.
- Our study included all oral fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin) prescribed in the US and the four most commonly prescribed non-fluoroquinolone antibiotics: amoxicillin, amoxicillin-clavulanate, azithromycin and cephalexin as controls.
- In addition to reporting the risk of any tendon rupture, we also reported the risk of three types of tendon ruptures by anatomic site 1) Achilles tendon rupture, 2) rupture of rotator cuff and 3) tendon ruptures on other anatomic sites as separate outcomes.
- This study is possibly only applicable to U.S. senior, aged 65 or more, Medicare fee-for-service beneficiaries.
- We had no options to verify claims diagnoses via chart review.

Introduction

Fluoroquinolones (FQ) are among the most widely prescribed antibiotics in the outpatient setting[1,2] due to their broad spectrum treatment of bacteria found in respiratory, urinary, joint, and skin infections. Several observational studies have reported the association between the use of FQs and tendinitis and tendon rupture (TR), especially of the Achilles tendon[3–12] and the U.S. Food and Drug Administration (FDA) issued black box warnings to FQ antibiotics beginning in 2008.[13] The warning was updated in 2016 to recommend using alternative antibiotics when possible.[14,15] The fact that FQs upregulate the production of metalloproteinase enzymes with collagenase activity that could weaken tendons is taken as a mechanism to explain this reported risk.[16–18]

Studies that reported association between FQ use and TR used one or more other antibiotics as controls. One study compared the FQ rupture rates with patients using azithromycin, the most frequently used oral antibiotic in the US. Only two focused principally on TR risk among the elderly. None compared TR rates of *FQs* with those of cephalexin -- the 3rd most commonly prescribed oral antibiotic in the US.

The Virtual Research Data Center (VRDC) of Center for Medicare and Medicaid Services (CMS)[19] carries more than 10 years of Medicare claims, which include information about the usage of prescription drugs and encounter diagnoses (including tendon ruptures). It also carries information about 42 major chronic conditions, demographic characteristic and vital status. We conducted a large observational study using the VRDC to assess the association of FQ antibiotics with TR compared to that of

the four most commonly prescribed non-FQ antibiotics in the US. Here we report the results of that analysis.

Methods

Patient and public involvement

Neither patients nor the public were not involved in the design of the study.

Study population

We derived our study population from a 20% random sample of Medicare prescription drug coverage (Part D) enrollees who first enrolled in the Medicare under old age and survivors insurance within a month of age 65 (779-781 month-old) and on or after 1/1/2007 - the first full year of Part D prescriptions availability. We included claim data through 12/31/2016, the end of VRDC claim data available to us. All of the VRDC data is de-identified and researchers must perform all of their analysis within the VRDC computer systems, and can only pull statistical results from it.[19] This study was declared not human subject research by the Office of Human Research Protection at the National Institutes of Health and by the CMS's Privacy Board.

We required subjects to be continuously enrolled in hospital insurance (Part A) and medical insurance (Part B) to assure we had full outpatient and inpatient claims data, which are not available for nearly 20% of subjects with Part D only.[20] To obtain a cohort of new TR patients, we excluded individuals with TRs recorded in the first year of their Medicare entitlement.[21] In order to assure sufficient follow-up, we excluded

individuals with less than 1-year follow-up. Moreover, to obtain incident (or new) drug user cohort, we excluded individuals who were prescribed any study antibiotics during their first 3-month after Part D enrollment, while ignoring the data during the same time window for individuals not taking study antibiotics. By doing so, we minimize survivor bias from a prevalent users (Figure 1 Consort Diagram).

Primary Outcome

We identified patients with TR based upon International Classification of Diseases (ICD)-9-CM codes of 726.13, 727.60-727.69, and ICD-10-CM codes of M66.2, M66.3, M66.8, M66.9, and M75.1. We combined all TRs and reported them as one outcome, and report three types of TRs by anatomic site 1) Achilles tendon rupture, 2) rupture of rotator cuff and 3) TRs on other anatomic sites as separate outcomes. We focused on Achilles TR because it was the sole focus of many prior studies and on rotator cuff TR because it is the predominant TR of the elderly. We lumped the remaining as "other TRs".

Study antibiotics

We included a total of seven study antibiotics prescribed in the US including all three oral FQs (moxifloxacin (MXF), ciprofloxacin (CIP), levofloxacin (LVX), the active stereoisomer of ofloxacin) and the four most frequently prescribed non-FQ oral antibiotics (amoxicillin (AMX), amoxicillin clavulanate (AMC), azithromycin (AZT) and cephalexin (LEX)) as a control. Ciprofloxacin and the four non-FQ, study antibiotics were the five most frequently used U.S. oral antibiotics in 2011.

Statistical Analysis

We analyzed each of the four TR outcomes in separate Fine-Gray competing risk regression analyses with death as the competing risk.[22,23] Individuals became eligible for "the study" at their Medicare enrollment but prescription data did not become available until their Part D enrollment. We followed them from their entry in Part D (while accounting for left truncation[24]) until their first diagnosis of TR, death, switch to a capitated plan, disenrollment from Medicare or 12/31/2016 – whichever came first. In each regression analysis, we included the seven antibiotics whose effects on TR were our primary interest. We adjusted hazard ratio (HR) of each study antibiotic for concurrent use of the other study antibiotics. We also adjusted for calendar year of individual's Part D entry, to account for secular trends, and their socio-demographic characteristics of gender, race, rural residency (Yes/No) and income status. We inferred individual's income level from the monthly indicators of dual-eligibility and Low Income Subsidy (LIS) status, which separate subjects into three groups; 1) dual whose income is below 135% Federal Poverty Line (FPL); 2) non-dual LIS whose income is between 135 and 150% FPL; and 3) non-dual no LIS whose income is above 150% FPL, respectively. We used this variable in the analysis as a surrogate for economic status.[25] We also included the 42 chronic conditions within the Medicare Master Beneficiary Summary File [26] that had >1% prevalence as measures of overall health. We assumed that patients were on a given study drug from the prescription dispensing date to the end of days of supply. We did not distinguish between different brands of a study drugs. Following the approach of prior studies,[3–5] we separated subjects by temporal exposure within each study drug,

including groups for never exposed, exposed within 30 days, 31-60 days, and >60 days of the index (or TR event) time. Thus, by this approach we could detect the presumed short term action of the FQ's on tendons and avoid the risk of non-differential misclassification that can occur with too simple (yes/no) drug exposure measures.[27] In order to minimize the immortal time bias, we treated all drug usage measures and all socio-demographic characteristics, except gender, race and rural residency, as time-varying covariates.[28,29] In order to mitigate selection bias toward use of any study antibiotics, we employed a propensity score (PS) approach.[30,31] We first derived a PS of taking any of study antibiotics as a function of individual's characteristics at the time of the first antibiotic use after Part D entry from a multiple logistic regression. We used the median days to the first study antibiotic use in patients taking study antibiotics as the cutoff time for individuals not taking study antibiotics. We performed our analyses with an inverse propensity score weight (IPSW) excluding individuals with the PS below 0.1 and above 0.9, to mitigate poorer performance in the presence of a strong treatment-selection process.[32] In post-hoc analyses, we also compared the risk of TR of each study antibiotics to that of every other study antibiotic on a pairwise basis.

Results

Study population and Secular trend

From our 20% sample of Part D enrollees, 1,009,925 individuals satisfied all our selection criteria including the washout of individuals with any antibiotic use in their first 3-month of Part D enrollment (Figure 1 Consort Diagram). Follow-up began with an individual's enrollment in Part D program (median (IQR) 0 (0-122) days from the

Medicare entitlement). We followed them for a median of 3.6 years (total 4,030,897 patient-years) until their first diagnosis of TR (3.5%), death (4.6%), switch to a capitated plan (12.6%), disenrollment from Medicare (<1%) or study end on 12/31/2016 (79.3%), whichever came first. Patients had their first post enrollment claim with a diagnosis of TR at a median age of 68.5 (IQR 67.2-70.4). The proportions of non-Hispanic White, female and rural residents were 80.7%, 57.0%, and 22.6% respectively. About a fifth of individuals received federal/state subsidies, i.e. Medicaid coverage on top of Medicare (dual 16.1%) or assistance in paying their Part D premium and coinsurance/copayment (non-dual LIS 2.7%). Among the 42 Medicare chronic conditions, hypertension (67.3%), hyperlipidemia (68.4%), cataract (46.4%), rheumatoid arthritis/osteoarthritis (36.6%), anemia (30.4%), ischemic heart disease (26.2%), and chronic kidney disease (17.9%) were the seven most prevalent (Table 1).

Of the 328,654 (33.0%) patients who ever took an FQ, 71.5%, 47.5% and 4.5% had taken CIP, LVX and MXF respectively. Of 576,885 (57.1%) of patients who ever took a non-FQ antibiotic, the figures were 53.6%, 44.9%, 33.9% and 31.1% for AZM, AMX, LEX, and AMC, respectively. Patients who took one or more study antibiotics took a median (IQR) of 3.0 (1.0-6.0) study antibiotic prescriptions and took a median (IQR) 2.0 (1.0-3.0) different study antibiotics during the observation period. About 2.5% patients who took one or more study antibiotics took one or more such antibiotics at the same time. Secular trends in study antibiotics usage existed (Supplementary Figure 1). MXF usage declined precipitously from 5.0% in 2007 to almost zero in 2016 – overweighting the MXF statistics for early entrants into Medicare and yielding a longer mean follow-up

time. CIP use hit a peak, and LVX, a nadir, in 2011. The use of AMX, AMC and LEX trended slowly upward (Supplementary Figure 1). The mode (median) of supply durations for each antibiotics were short--10 (7) for AMX, 10 (10) for AMC, 5 (5) for AZM, 10 (7) for LEX, 7 (7) for CIP, 10 (7) for LVX, 10 (11) for MXF. About 35% of individuals were never exposed to any of the study antibiotics during the study period.

Unadjusted figures for TR prevalence across each of the seven study antibiotic users and the no study antibiotic users ranged from a high of 5.2% for MXF to a low of 2.9% for no antibiotic (Table 1). Except for MXF, the *unadjusted* prevalence of TRs associated with each non-FQ antibiotic was *greater than* or equal to that of each FQ antibiotic. The TR rates per 1000 patient-years followed the same pattern, with the non-FQ antibiotics topping the rates of all FQs except MXF (with the highest rate), possibly due to overweighting of MXF usage in the early years of the study. Patients who ever took an FQ had the highest unadjusted rate of death per 1000 person-years. LVX's death rate was nearly twice the rate of each non-FQ antibiotics. The size of the associations with conditions like diabetes, chronic renal failure and heart failure paralleled the magnitude of the death rates and was generally higher with FQs than non-FQ antibiotics (Table 1).

Primary Analysis

Table 2 presents HRs for all non-antibiotic covariates in our Fine-Gray competing risk regression with IPSW. For simplicity sake, in Table 2, we report the HRs of all anatomic types of tendon ruptures taken together. Being a female (vs. male), African-American, Hispanic, and Asian (vs. white), being dual or non-dual LIS (vs. non-dual no LIS) and

living in a rural area were all associated with a *reduced* risk of tendon rupture. These risk reductions were 24% or more for all but Hispanics and rural residency covariates, and the reductions were similar across all anatomic sites. In general, life-threatening chronic conditions, such as AMI, COPD, heart failure and colorectal/lung/endometrial cancers were associated with a lower risk of TR in a range of 15-60% below control possibly due to constrained physical activity and/or shortened life span. Notably, diabetes and chronic renal disease, previously reported as risk factors for TR,[33,34] exhibited no increased TR risk. Mobility impairments had reduced risk of TR similar to that of the severe life-threatening conditions, likely due to reduced activity. Most conditions with low life threats such as cataract, glaucoma, depression, asthma, hyperlipidemia, hypertension, prostatic hyperplasia, migraine/other chronic headache, and deafness/hearing impairment exhibited risks of 8 to 34% *above* controls probably for reasons related to longer life spans and less inhibited activity. Ischemic heart did not fit the mold of sicker equals lower TR risk. Patients with rheumatoid arthritis/osteoarthritis were a special case and had TR risk of 184% *above* control possibly due to joint and associated tendon inflammation with these disorders. Fibromyalgia/chronic pain and fatigue also exhibited a 39% increased risk of TR possibly also due to an inflammatory component.

The Achilles tendon carries the full force of the extra weight carried by obese patients and obesity was associated with a significant (13%) increase in Achilles TR ruptures while its effect on other TR classes was significant but miniscule (2-3%) (Data not shown).

Effect of antibiotics

We report HRs from our primary analysis in tables separate from the non-antibiotic covariates. Table 3 shows the risk associated with each study antibiotic broken down by time lag between the antibiotic use and the TRs (separate rows), and by all TRs together and separately by anatomic sites (in columns). We also report HRs of death (competing risk). We used multiplicity corrected p-values to simultaneously test the difference of pairs of antibiotics to minimize the chance of finding statistically significant difference by random chance.[35] Of the total 34,880 patients with any TR occurrence, complete rupture of rotator cuff represented the major share (80.5%), followed by other TRs (16.9%) and Achilles TR (2.6%). In the survival analysis, we followed patients until the first occurrence of TR; so, these figures count only the first TR occurrence independent of anatomic site.

Of the non-FQ antibiotics, AMX exhibited a reduced risk of TR compared to no AMX in every tendon class and time window, similar to its low risk in previous studies. It exhibited a significantly lower risk in the ≤30-day window except for the Achilles tendon. AZM and AMC exhibited a similar benign risk in all time windows except for TR of rotator cuff in >60-day window. LEX was the surprise non-FQ antibiotic. It exhibited modest to large *increase*d TR risk at ≤30-day window across all sites ranging from a low of 19% increase for complete rupture of rotator cuff to a high 93% increase for Achilles TR. Its risk was also significantly higher at ≤30-day window for all TRs taken together.

Of the FQs, CIP and MXF, the most and least frequently prescribed FQ, exhibited little to no increased risk of TR within each anatomic site and each time frame. LVX is the only FQ to exhibit a significant *increase* in TR risk - of 16%, and 120% for rupture of rotator

cuff and Achilles TR respectively in the ≤30-day window. Notably, the risk of LVX never exceeded the risk of the non-FQ, LEX in any comparison.

In a post-hoc analysis (Table 4), we compared the TR risk of each antibiotic with every other antibiotic (pairwise comparisons of FQ vs. FQ and FQ vs. non-FQ), for ≤30-day window and FQs as a class vs. each non-FQ after combining the data from the three time windows. These results paralleled the above-mentioned risk for each study antibiotic in Table 3. Again, TR risk for LVX was greater than that of CIP, MXF, AMC, AMX, and AZM in a ≤30-day window. However, LVX risk was comparable to that of LEX for Achilles TR, and rupture of rotator cuff and significantly lower than LEX for the other TR classes. When comparing the risk of FQs as a class against that of non-FQ antibiotics, most of the non-FQ antibiotics had significantly greater risk than the FQ class as a whole across all TR sites (See last 4 rows of Table 4).

In another analysis evaluating risk of death for each antibiotics, each FQ antibiotic exhibited a significant increase in death risk of – 46% (for CIP), 105% (for MXF) and 119% (for LVX) in a ≤30-day window. Among non-FQ antibiotics, only AMC exhibited 37% increased risk of death in a ≤30-day window. Overall, risk of death for FQs as a class far outweighed that of each non-FQ antibiotics.

Discussion

Our results conflict with the common assertion that the Achilles tendon rupture is the most common tendon rupture (up to 90% in one report[36]). In our elderly cohort, Achilles TRs were a tiny, 2.6%, of all TRs. Some of this difference may be explained by

the differences in demographics. Reports of high prevalence of Achilles TR came from studies of young military populations.[37,38] In contrast, our data came from an elderly Medicare population. Some of the difference could also be due to less ability to diagnose non-Achilles tendon ruptures until MRI joint imaging became widely available, because such TRs are less amenable to diagnosis by physical exam.

Many authorities describe the relationship between FQs and TRs as a class "effect". However, FQs as a class had no significant risk of TR compared with each of the four non-FQ antibiotics in any time window. CIP (n=234,994 subjects) is the oral FQ with the greatest use and with a greater effect on metalloproteases than other FQs.[39–41] However, neither MXF (n= 14,728 subjects) nor CIP had any TR risk at any anatomic site in any time window. CIP's lack of risk is consistent with two studies[5,9] in which CIP exhibited zero risk or small risks compared to ofloxacin, a racemic mixture whose active ingredient is the levo-isomer, LVX. We do see a strong association between LVX and TRs whether we used no LVX or three of the non-FQ antibiotics as controls. However, when we used LEX, a cephalosporin, as the control for LVX's effect on TRs, we saw no increased risk.

As noted in the introduction, the FDA has added a black box warning about tendon ruptures to the labels of fluoroquinolones. A 2015 paper[42] described the evidence for this decision based on the FDA's Adverse Event Reporting System (FAERS) database and an empirical Bayes geometric mean (EBGM) score, which is based on the relative frequency of spontaneous report about a given adverse event in one drug versus the

reporting of that adverse event across all drugs. This EBGM score based upon FAERS database has been useful but FAERS database is still limited by a lack of true denominator for population at risk, underreporting due to a voluntary reporting scheme and bias due to limited adjustment variables.[43] Our study was based on a well-defined Medicare population with 80 variable adjustments. The fact that levofloxacin's EBGM score was six times that of ofloxacin[42] though both drugs have the same active ingredient (the levo-isomer of ofloxacin) and the same dose of that ingredient, raises questions about what factors influenced that score.

One previous study described the effect of FQs on TR risk as small and unimportant.[10] Two studies reported no effect of FQs on TR risk.[9,11] At least 7 observational studies reported that the use of FQs increased risks of TR.[3–8,12] However, in all but one study, the number of TRs among patients taking an FQs was small (between 5 and 111). In comparison, our study included 12,517 (3.8%) such patients. One previous study did report a large number of TR events, 23,000 (3.5%) patients while on FQs and, like our study, it focused exclusively on elderly patients.[3] However, it did not compare the population of FQ users against non-users but FQ usage periods against non-usage periods in the same set of patients, which were likely periods without visits and thus could not account for the effect of increased clinical attention provided at visits requiring a strong systemic antibiotic. Furthermore, they assessed the association between AMX and TRs in separate analysis and used the risk of TRs in that analysis as the comparator for the risk observed in the FQ analysis. Finally, their analysis did not include death as a competing

risk as is recommend when death rates exceed event rates[23] which was likely the case because in the demographics of their study was very similar to ours.

In our study, AMX treated patients exhibited a similar absolute risk of TR as to LVX treated patients (7.56 vs. 7.47 per 1000 patient-years). However, they had fewer comorbidities (as in Daneman's study), almost 14% fewer hospitalizations and half of death rate, compared to patients taking LVX (7.56 vs. 18.50 per 1000 patient-years). So the two populations are not comparable. LVX exhibited 119% increased risk of death in a ≤30-day window. They appears to be reserved for more severe infections or more fragile patients and thus subject to differential biases.

The reported activation of metalloprotease activity by FQs has underpinned the idea of a causal link between FQs and TRs. The argument goes as follows: FQs stimulate metalloproteases, which can break down collagen; the tendon is made of collagen; so FQs may cause TRs. However, our data disrupts this argument. CIP which strongly *stimulates* metalloprotease activity,[17,18] exhibited *no* risk of TRs in our study, and LEX which *inhibits* metalloprotease activity[44,45] exhibited a *large* risk. So we have to question whether metalloprotease activity has any relevance to TR risk, and consider other explanations for the observed associations.

The indication for an antibiotic is a presumed bacterial infection. The reported associations between antibiotics and TR could be a consequence of the indication (infection) rather than the antibiotic use to treat it. It could be a perfects example of the

confounding by indication.[46] Such a bias could explain many reported associations between drugs and TR risk including associations with non-antibiotic drugs reported by Nyyssönen.[8]

This indication (and infection) bias could generate an association between the antibiotic and TRs in different ways. First, the bacterial infection might directly increase the risk of TR via stimulation of general immune or cytokine responses, or even by direct bacterial invasion. A recent study found gram-positive bacteria in a major share of ruptured tendons but not in "control" tendons removed surgically for grafting,[47] So the possibility of direct invasion of tendons by circulating bacteria with subsequent weakening and rupture is plausible.

Secondly, the greater clinical attention likely focused on patients needing systemic antibiotics, especially those with more severe infections, could increase the chance of noticing and documenting a pre-existing TR. A reservoir of not-yet-diagnosed such cases is likely to exist, because patients do not necessarily correctly identify joint and extremity symptoms as TRs and seek immediate care for them. Tendon ruptures of the shoulder capsule, for example, are notorious for developing symptoms slowly over 2-3 years[48] before being correctly diagnosed. Even Achilles tendon ruptures, can be missed (in 30% of cases) at the first presentation.[49] Seeger et al. reviewed the medical records of patients with an insurance claim reporting TRs following antibiotic use and found that nearly half of the TRs recorded in the claims were either something else (e.g., Bursa

inflammation miscoded as a TR) or had occurred pre antibiotic use but only seen in a claim post antibiotic use.[11]

Indication bias is a plausible explanations for associations reported in observational studies and it should be considered more often before assuming the associations are causal.

Limitation

This study faces all of the limitations of observational studies. Furthermore, it applies only to fee-for-service Medicare populations. In addition, we had no options to verify claims diagnoses via chart review. From a statistical point of view, our findings may have some limitations. First, we included 80 covariates in one analysis and concern about possibly strong intercorrelation affecting the validity could exist. To evaluate the intercorrelation among covariates, we calculated an 80x80 correlation matrix of estimated regression coefficients from our competing risk regression analysis considering their time-varying nature. The correlation matrix can deliver information about the strength of all pairwise correlation and indicate the existence of a collinear relationship between two predictors. All correlations (except diagonal elements) were below 0.5, only 1.6% were between 0.2 and 0.5. The largest of the pairwise correlations was 0.33 indicating minimal bias due to intercorrelation. We also did not consider interactions among covariates in our analysis because of the enormous number of two way interactions (as large as 6,400) and thus the problem of overfitting.

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Competing interests Statement

All authors have no competing interest to declare.

Contributorship Statement

SB: study conception, design, analysis and interpretation; critical review of study content; manuscript drafting; approval of the final manuscript. JL: study concept and interpretation; manuscript drafting; approval of the final manuscript. VH: study interpretation; manuscript drafting; approval of the final manuscript. CJM: study conception, design and interpretation; critical review of study content; manuscript drafting; approval of the final manuscript.

Data availability

The authors confirm that the data supporting the findings of this study are available within the article [and/or] its supplementary materials.

Patient Consent for publication: Not required.

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Figure 1. Consort Diagram

Table 1. Outcome, Medical/Medication Use, Diseases and Patient Characteristics by Type of Antibiotics

Variable	Overall	FLQ	CIP	LVX	MXF	AMX	AZM	LEX	AMC	None
N	1,009,925	328,654	234,994	155,991	14,728	259,125	308,985	195,731	179,616	356,364
Tendon Rupture	34,880(3.5)	12,517(3.8)	8,811(3.7)	5,904(3.8)	770(5.2)	9,636(3.7)	12,448(4.0)	8,019(4.1)	6,622(3.7)	10,169(2.9)
Death	46,468(4.6)	23,249(7.1)	14,821(6.3)	14,610(9.4)	2,136(14.5)	9,632(3.7)	14,608(4.7)	11,394(5.8)	9,951(5.5)	13,645(3.8)
Censored at HMO entry	127,162(12.6)	27,573(8.4)	19,847(8.4)	11,142(7.1)	1,571(10.7)	21,215(8.2)	26,140(8.5)	14,887(7.6)	12,674(7.1)	65,886(18.5)
Censored at disenrollment	145(0.0)	25(0.0)	13(0.0)	13(0.0)	2(0.0)	19(0.0)	27(0.0)	23(0.0)	16(0.0)	85(0.0)
Censored at Dec 31 2016	801,270(79.3)	265,290(80.7)	191,502(81.5)	124,322(79.7)	10,249(69.6)	218,623(84.4)	255,762(82.8)	161,408(82.5)	150,353(83.7)	266,579(74.8)
Years of follow-up, median(total)	3.6(4,030,897)	4.6(1,620,894)	4.8(1,190,308)	4.8(789,849)	6.0(87,397)	4.5(1,274,357)	4.6(1,529,370)	4.8(1,000,459)	4.6(890,340)	2.5(1,067,731)
Tendon rupture, 1000 person-years	8.65	7.72	7.40	7.47	8.81	7.56	8.14	8.02	7.44	9.52
Death, 1000 person-years	11.53	14.34	12.45	18.50	24.44	7.56	9.55	11.39	11.18	12.78
Female	575,885(57.0)	197,915(60.2)	146,745(62.4)	89,682(57.5)	8,747(59.4)	151,383(58.4)	194,101(62.8)	113,308(57.9)	104,749(58.3)	191,069(53.6)
White	814,933(80.7)	274,785(83.6)	196,048(83.4)	131,725(84.4)	12,464(84.6)	215,101(83.0)	259,657(84.0)	167,825(85.7)	153,723(85.6)	271,906(76.3)
Black	75,930(7.5)	20,017(6.1)	14,286(6.1)	8,893(5.7)	956(6.5)	15,622(6.0)	17,296(5.6)	9,625(4.9)	9,199(5.1)	35,023(9.8)
Hispanic	56,582(5.6)	17,044(5.2)	12,607(5.4)	7,943(5.1)	628(4.3)	12,494(4.8)	14,805(4.8)	8,976(4.6)	7,802(4.3)	24,391(6.8)
Asian	26,336(2.6)	7,316(2.2)	5,362(2.3)	3,144(2.0)	356(2.4)	7,624(2.9)	7,945(2.6)	3,539(1.8)	3,440(1.9)	10,437(2.9)
Other	36,144(3.6)	9,492(2.9)	6,691(2.8)	4,286(2.7)	324(2.2)	8,284(3.2)	9,282(3.0)	5,766(2.9)	5,452(3.0)	14,607(4.1)
Ever Dual	162,988(16.1)	54,055(16.4)	38,277(16.3)	28,156(18.0)	2,908(19.7)	35,305(13.6)	44,940(14.5)	30,962(15.8)	25,255(14.1)	66,986(18.8)
Non-Dual LIS	26,955(2.7)	7,648(2.3)	5,459(2.3)	3,746(2.4)	385(2.6)	5,224(2.0)	6,828(2.2)	4,191(2.1)	3,818(2.1)	12,595(3.5)
Non-Dual No LIS	819,982(81.2)	266,951(81.2)	191,258(81.4)	124,089(79.5)	11,435(77.6)	218,596(84.4)	257,217(83.2)	160,578(82.0)	150,543(83.8)	276,783(77.7)
Living in rural area	228,199(22.6)	78,581(23.9)	56,385(24.0)	38,847(24.9)	2,801(19.0)	58,805(22.7)	72,282(23.4)	49,977(25.5)	42,288(23.5)	77,087(21.6)
Days on Rx, median (IQR)	N/A	N/A	10.0(7.0-20.0)	10.0(7.0-17.0)	10.0(7.0-12.0)	10.0(7.0-20.0)	5.0(5.0-11.0)	10.0(7.0-16.0)	10.0(10.0-20.0)	N/A
Hospitalization	349,959(29.5)	198,846(45.4)	142,538(45.3)	113,829(52.5)	14,002(60.3)	132,304(38.8)	156,185(37.9)	119,209(45.9)	103,515(42.5)	51,525(14.4)
Outpatient visits per year, median (IQR)	19.6(11.1-33.0)	27.1(17.2-42.7)	27.3(17.5-42.9)	30.1(19.0-47.8)	34.0(21.7-53.7)	23.6(14.5-37.5)	24.6(15.5-38.8)	27.5(17.2-43.2)	26.6(16.7-42.2)	12.3(6.0-21.8)
AMI	21,222(2.1)	9,999(3.0)	6,810(2.9)	5,862(3.8)	698(4.7)	6,474(2.5)	8,079(2.6)	6,215(3.2)	5,292(2.9)	5,012(1.4)
Atrial Fibrillation	71,635(7.1)	31,752(9.7)	21,757(9.3)	17,731(11.4)	2,028(13.8)	23,974(9.3)	26,182(8.5)	21,935(11.2)	18,764(10.4)	16,314(4.6)
Cataract	468,608(46.4)	183,870(55.9)	134,196(57.1)	88,574(56.8)	9,216(62.6)	144,455(55.7)	174,897(56.6)	112,020(57.2)	101,079(56.3)	124,931(35.1)
Chronic Kidney Disease	180,441(17.9)	86,021(26.2)	62,323(26.5)	46,121(29.6)	4,651(31.6)	53,713(20.7)	65,577(21.2)	50,361(25.7)	43,182(24.0)	42,916(12.0)
COPD	130,840(13.0)	71,913(21.9)	43,961(18.7)	48,430(31.0)	6,106(41.5)	40,109(15.5)	66,536(21.5)	37,413(19.1)	37,579(20.9)	22,739(6.4)
Heart Failure	103,010(10.2)	51,814(15.8)	34,870(14.8)	31,377(20.1)	3,776(25.6)	32,792(12.7)	41,647(13.5)	31,585(16.1)	27,223(15.2)	21,907(6.1)
Diabetes	284,919(28.2)	113,424(34.5)	81,175(34.5)	57,697(37.0)	5,942(40.3)	81,155(31.3)	98,176(31.8)	67,548(34.5)	59,984(33.4)	81,448(22.9)
Glaucoma	150,839(14.9)	56,990(17.3)	41,984(17.9)	26,603(17.1)	2,930(19.9)	45,597(17.6)	54,726(17.7)	33,936(17.3)	31,065(17.3)	42,355(11.9)
Hip/Pelvic Fracture	7,982(0.8)	4,086(1.2)	3,000(1.3)	2,289(1.5)	274(1.9)	2,673(1.0)	3,005(1.0)	2,515(1.3)	1,914(1.1)	1,689(0.5)
Ischemic Heart Disease	264,648(26.2)	117,416(35.7)	82,182(35.0)	63,659(40.8)	6,956(47.2)	83,682(32.3)	101,999(33.0)	70,612(36.1)	63,363(35.3)	63,372(17.8)
Depression	210,714(20.9)	94,554(28.8)	68,625(29.2)	49,277(31.6)	5,298(36.0)	65,642(25.3)	83,253(26.9)	56,747(29.0)	51,150(28.5)	49,320(13.8)
Alzheimer's Disease or Senile Dementia	39,132(3.9)	19,796(6.0)	14,309(6.1)	11,030(7.1)	1,206(8.2)	11,140(4.3)	13,809(4.5)	11,846(6.1)	9,309(5.2)	9,400(2.6)
Osteoporosis	106,966(10.6)	47,033(14.3)	35,217(15.0)	22,918(14.7)	2,738(18.6)	34,610(13.4)	44,016(14.2)	26,996(13.8)	24,393(13.6)	25,216(7.1)

Rheumatoid Arthritis/Osteoarthritis	369,584(36.6)	160,091(48.7)	117,018(49.8)	80,115(51.4)	8,259(56.1)	126,702(48.9)	148,653(48.1)	101,310(51.8)	88,017(49.0)	81,855(23.0)
Stroke/Transient Ischemic Attack	58,886(5.8)	27,702(8.4)	19,843(8.4)	15,051(9.6)	1,670(11.3)	17,829(6.9)	22,038(7.1)	16,684(8.5)	14,245(7.9)	14,262(4.0)
Breast Cancer	45,316(4.5)	19,362(5.9)	14,344(6.1)	9,442(6.1)	984(6.7)	13,451(5.2)	17,676(5.7)	12,543(6.4)	10,156(5.7)	11,042(3.1)
Colorectal Cancer	15,905(1.6)	7,487(2.3)	5,421(2.3)	4,048(2.6)	390(2.6)	4,304(1.7)	5,170(1.7)	4,085(2.1)	3,605(2.0)	4,104(1.2)
Prostate Cancer	37,038(3.7)	19,705(6.0)	15,577(6.6)	9,232(5.9)	643(4.4)	10,967(4.2)	11,733(3.8)	9,252(4.7)	8,070(4.5)	8,333(2.3)
Lung Cancer	14,946(1.5)	8,965(2.7)	5,144(2.2)	6,356(4.1)	905(6.1)	3,859(1.5)	6,633(2.1)	3,977(2.0)	4,267(2.4)	2,733(0.8)
Endometrial Cancer	7,396(0.7)	3,447(1.0)	2,670(1.1)	1,635(1.0)	160(1.1)	2,095(0.8)	2,637(0.9)	1,957(1.0)	1,604(0.9)	1,847(0.5)
Anemia	307,310(30.4)	140,606(42.8)	100,819(42.9)	74,308(47.6)	7,980(54.2)	99,190(38.3)	118,327(38.3)	81,967(41.9)	72,587(40.4)	71,098(20.0)
Asthma	86,120(8.5)	46,350(14.1)	29,327(12.5)	30,152(19.3)	4,091(27.8)	27,632(10.7)	46,823(15.2)	24,426(12.5)	25,465(14.2)	13,802(3.9)
Hyperlipidemia	691,148(68.4)	257,086(78.2)	185,199(78.8)	123,828(79.4)	12,162(82.6)	199,236(76.9)	239,414(77.5)	152,879(78.1)	140,364(78.1)	201,258(56.5)
Hyperplasia	122,010(12.1)	59,809(18.2)	45,517(19.4)	28,616(18.3)	2,587(17.6)	39,031(15.1)	42,070(13.6)	31,606(16.1)	28,398(15.8)	27,336(7.7)
Hypertension	679,287(67.3)	253,601(77.2)	181,231(77.1)	124,646(79.9)	12,218(83.0)	192,686(74.4)	230,409(74.6)	150,995(77.1)	136,292(75.9)	201,777(56.6)
Hypothyroidism	197,447(19.6)	81,468(24.8)	59,450(25.3)	40,372(25.9)	4,198(28.5)	59,893(23.1)	76,582(24.8)	47,973(24.5)	44,249(24.6)	50,280(14.1)
Anxiety Disorders	148,983(14.8)	70,688(21.5)	51,377(21.9)	37,563(24.1)	4,032(27.4)	48,859(18.9)	62,418(20.2)	41,655(21.3)	37,588(20.9)	31,709(8.9)
Bipolar Disorder	17,882(1.8)	8,368(2.5)	6,104(2.6)	4,533(2.9)	468(3.2)	5,442(2.1)	6,658(2.2)	5,147(2.6)	4,227(2.4)	4,242(1.2)
Major Depressive Affective Disorder	153,182(15.2)	71,732(21.8)	52,101(22.2)	38,055(24.4)	4,148(28.2)	48,846(18.9)	61,872(20.0)	43,416(22.2)	38,642(21.5)	33,660(9.4)
Schizophrenia and other Psychotic Disorders	16,764(1.7)	8,591(2.6)	6,176(2.6)	4,934(3.2)	548(3.7)	4,421(1.7)	5,597(1.8)	5,101(2.6)	3,811(2.1)	4,300(1.2)
Epilepsy	16,155(1.6)	7,543(2.3)	5,383(2.3)	4,269(2.7)	415(2.8)	4,310(1.7)	5,488(1.8)	4,510(2.3)	3,621(2.0)	4,191(1.2)
Fibromyalgia, Chronic Pain and Fatigue	166,279(16.5)	78,877(24.0)	57,494(24.5)	41,843(26.8)	4,410(29.9)	56,152(21.7)	70,667(22.9)	48,422(24.7)	43,379(24.2)	33,843(9.5)
Viral Hepatitis (General)	11,969(1.2)	4,659(1.4)	3,188(1.4)	2,523(1.6)	287(1.9)	3,156(1.2)	3,732(1.2)	2,712(1.4)	2,348(1.3)	3,735(1.0)
Liver Disease Cirrhosis and other Liver Conditions	62,675(6.2)	31,930(9.7)	23,284(9.9)	17,386(11.1)	1,919(13.0)	19,624(7.6)	24,544(7.9)	17,393(8.9)	15,958(8.9)	13,350(3.7)
Leukemias and Lymphomas	13,906(1.4)	7,228(2.2)	4,822(2.1)	4,536(2.9)	551(3.7)	4,385(1.7)	5,905(1.9)	4,025(2.1)	3,969(2.2)	2,758(0.8)
Migraine and other Chronic Headache	31,628(3.1)	14,936(4.5)	11,282(4.8)	7,520(4.8)	873(5.9)	10,841(4.2)	13,893(4.5)	8,763(4.5)	8,403(4.7)	6,419(1.8)
Mobility Impairments	20,600(2.0)	10,182(3.1)	7,356(3.1)	5,767(3.7)	577(3.9)	5,372(2.1)	6,629(2.1)	5,995(3.1)	4,610(2.6)	5,439(1.5)
Obesity	185,101(18.3)	79,130(24.1)	56,609(24.1)	41,226(26.4)	3,997(27.1)	58,654(22.6)	69,611(22.5)	49,984(25.5)	43,740(24.4)	44,772(12.6)
Peripheral Vascular Disease	90,132(8.9)	45,276(13.8)	31,866(13.6)	25,977(16.7)	3,001(20.4)	28,747(11.1)	36,241(11.7)	28,343(14.5)	23,977(13.3)	18,446(5.2)
Tobacco Use Disorders	101,890(10.1)	45,304(13.8)	28,907(12.3)	27,202(17.4)	3,042(20.7)	27,261(10.5)	37,860(12.3)	25,002(12.8)	22,975(12.8)	26,896(7.5)
Pressure Ulcers and Chronic Ulcers	30,345(3.0)	17,688(5.4)	12,800(5.4)	10,603(6.8)	1,196(8.1)	9,006(3.5)	10,926(3.5)	13,404(6.8)	9,960(5.5)	4,992(1.4)
Deafness and Hearing Impairment	59,576(5.9)	27,383(8.3)	19,976(8.5)	14,014(9.0)	1,609(10.9)	21,213(8.2)	25,498(8.3)	16,849(8.6)	16,787(9.3)	11,900(3.3)

Note. Data are presented as No. (%) of patients unless otherwise noted.
Abbreviations: FLQ, fluoroquinolone; CIP, ciprofloxacin; LVX, levofloxacin; MXF, moxifloxacin; AMX, Amoxicillin; AMC, Amoxicillin Clavulanate; AZT, Azithromycin; LEX, Cephalexin; IQR, interquartile range.

Table 2. Hazard Ratios of Tendon Rupture for Each Covariate

Variables	Reference	HR(95% CI)
Female	Male	0.70(0.69,0.72)↓
Black	White	0.76(0.73,0.78)↓
Hispanic		0.91(0.87,0.94)↓
Asian		0.67(0.63,0.71)↓
Other		1.05(1.01,1.09)↑
Dual Ever	Non-Dual Non-LIS	0.66(0.64,0.68)↓
Non-Dual Lis		0.66(0.63,0.70)↓
Living In Rural Area	No	0.94(0.92,0.95)↓
Medicare Part D Since 2008	Medicare Part D Since 2007	1.03(1.00,1.07)
Medicare Part D Since 2009		1.11(1.07,1.15)↑
Medicare Part D Since 2010		1.16(1.12,1.21)↑
Medicare Part D Since 2011		1.17(1.13,1.22)↑
Medicare Part D Since 2012		1.12(1.08,1.16)↑
Medicare Part D Since 2013		1.03(1.00,1.07)
Medicare Part D Since 2013		1.05(1.01,1.09)↑
Medicare Part D Since 2015		0.91(0.87,0.96)↓
Medicare Part D Since 2016		0.93(0.19,4.55)
AMI	No	0.74(0.69,0.79)↓
Atrial Fibrillation	No	0.94(0.91,0.97)↓
Cataract	No	1.23(1.21,1.25)↑
Chronic Kidney Disease	No	0.92(0.89,0.94)↓
COPD	No	0.83(0.81,0.86)↓
Heart Failure	No	0.79(0.77,0.82)↓
Diabetes	No	0.98(0.96,0.99)↓
Glaucoma	No	1.10(1.08,1.12)↑
Hip/Pelvic Fracture	No	0.68(0.60,0.77)↓
Ischemic Heart Disease	No	1.10(1.08,1.12)↑
Depression	No	1.17(1.13,1.21)
Alzheimer's Disease or Senile Dementia	No	0.67(0.63,0.71)↓
Osteoporosis	No	1.03(1.01,1.06)↑
Rheumatoid Arthritis/Osteoarthritis	No	2.84(2.80,2.89)↑
Stroke/Transient Ischemic Attack	No	0.97(0.94,1.01)
Breast Cancer	No	0.94(0.91,0.98)↓
Colorectal Cancer	No	0.79(0.74,0.85)↓

Prostate Cancer	No	1.03(0.99,1.07)
Lung Cancer	No	0.39(0.34,0.45)↡
Endometrial Cancer	No	0.85(0.77,0.94)↓
Anemia	No	1.01(0.99,1.03)
Asthma	No	1.27(1.24,1.31)↟
Hyperlipidemia	No	1.34(1.31,1.36)↟
Hyperplasia	No	1.13(1.10,1.16)↟
Hypertension	No	1.09(1.07,1.11)↟
Hypothyroidism	No	1.08(1.06,1.10)↟
Anxiety Disorders	No	0.98(0.96,1.01)
Bipolar Disorder	No	1.02(0.95,1.08)
Major Depressive Affective Disorder	No	1.06(1.02,1.10)↑
Schizophrenia and Other Psychotic Disorders	No	0.67(0.61,0.74)↡
Epilepsy	No	0.83(0.77,0.90)↡
Fibromyalgia, Chronic Pain and Fatigue	No	1.39(1.36,1.42)↟
Viral Hepatitis (General)	No	1.04(0.96,1.13)
Liver Disease Cirrhosis And Other Liver Conditions	No	0.95(0.92,0.99)↓
Leukemias and Lymphomas	No	0.94(0.88,1.01)
Migraine and Other Chronic Headache	No	1.28(1.23,1.33)↟
Mobility Impairments	No	0.70(0.65,0.76)↡
Obesity	No	1.04(1.02,1.06)↑
Peripheral Vascular Disease	No	1.00(0.97,1.04)
Tobacco Use Disorders	No	0.82(0.80,0.85)↡
Pressure Ulcers and Chronic Ulcers	No	0.82(0.77,0.87)↡
Deafness and Hearing Impairment	No	1.21(1.17,1.25)↟

Hazard ratios and confidence intervals from the primary analysis for Covariates except for the study antibiotics (which are in Table 3)

Abbreviations: HR, hazard ratio, CI, confidence interval; FLQ, fluoroquinolone; CIP, ciprofloxacin; LVX, levofloxacin; MXF, moxifloxacin; AMX, Amoxicillin; AMC, Amoxicillin Clavulanate; AZT, Azithromycin; LEX, Cephalexin.

↟= significantly high with P-value < 0.001, ↑= significantly high with 0.001 ≤ P-value < 0.05
↡= significantly low with P-value < 0.001, ↓= significantly high with 0.001 ≤ P-value < 0.05

Table 3. Hazard Ratios of Each Antibiotic by Anatomic Sites and Temporal Order of Drug Exposure

		Any Tendon Rupture	Achilles Tendon Rupture	Complete Rupture of Rotator Cuff	Other Tendon Ruptures	Death (Competing risk)
	Temporal Exposure	HR(95% CI)	HR(95% CI)	HR(95% CI)	HR(95% CI)	HR(95% CI)
AMX VS. NO AMX	≤ 30 days	0.86(0.80,0.92)↓	0.88(0.59,1.33)	0.88(0.82,0.95)↓	0.79(0.67,0.93)↓	0.66(0.61,0.71)↓
	31 – 60 days	0.94(0.87,1.01)	0.80(0.49,1.31)	0.91(0.84,0.99)↓	1.08(0.93,1.27)	0.69(0.63,0.75)↓
	≥ 61 days	1.00(0.98,1.02)	0.99(0.86,1.13)	1.01(0.99,1.04)	0.97(0.92,1.01)	0.77(0.75,0.78)↓
AMC VS. NO AMC	≤ 30 days	0.93(0.85,1.02)	1.25(0.79,1.97)	0.87(0.79,0.97)↓	1.17(0.98,1.41)	1.37(1.30,1.45)↑
	31 – 60 days	0.95(0.85,1.05)	1.37(0.82,2.29)	0.95(0.84,1.06)	0.81(0.63,1.04)	1.26(1.17,1.35)↑
	≥ 61 days	1.07(1.04,1.09)↑	0.95(0.81,1.12)	1.07(1.04,1.10)↑	1.02(0.96,1.08)	0.86(0.84,0.88)↓
AZM VS. NO AZM	≤ 30 days	0.99(0.93,1.06)	1.15(0.82,1.63)	1.00(0.93,1.08)	0.87(0.75,1.01)	0.80(0.75,0.84)↓
	31 – 60 days	0.90(0.84,0.98)↓	0.99(0.65,1.49)	0.91(0.84,0.99)↓	0.95(0.81,1.11)	0.77(0.73,0.82)↓
	≥ 61 days	1.07(1.05,1.09)↑	1.02(0.91,1.15)	1.09(1.07,1.12)↑	0.99(0.95,1.04)	0.71(0.70,0.72)↓
LEX VS. NO LEX	≤ 30 days	1.31(1.22,1.41)↑	1.93(1.35,2.75)↑	1.19(1.09,1.29)↑	1.79(1.56,2.06)↑	1.04(0.98,1.10)
	31 – 60 days	1.05(0.95,1.15)	1.14(0.66,1.96)	1.06(0.96,1.18)	1.02(0.82,1.26)	1.01(0.94,1.08)
	≥ 61 days	1.08(1.05,1.11)↑	1.00(0.85,1.16)	1.07(1.05,1.10)↑	1.15(1.09,1.21)↑	0.86(0.84,0.88)↓
LVX VS. NO LVX	≤ 30 days	1.14(1.05,1.25)↑	2.20(1.50,3.24)↑	1.16(1.06,1.28)↑	0.96(0.78,1.19)	2.19(2.11,2.28)↑
	31 – 60 days	1.09(0.98,1.21)	1.91(1.17,3.10)↑	1.09(0.97,1.22)	1.14(0.90,1.43)	1.80(1.71,1.89)↑
	≥ 61 days	1.02(1.00,1.05)	1.22(1.03,1.43)↑	1.03(1.00,1.07)↑	0.97(0.91,1.03)	0.99(0.97,1.01)
CIP VS. NO CIP	≤ 30 days	0.96(0.89,1.03)	1.06(0.70,1.60)	0.96(0.88,1.04)	0.84(0.71,1.00)↓	1.46(1.40,1.53)↑
	31 – 60 days	0.92(0.85,1.01)	1.02(0.63,1.67)	0.91(0.82,1.00)↓	0.95(0.78,1.14)	1.31(1.24,1.38)↑
	≥ 61 days	0.96(0.94,0.98)↓	1.16(1.02,1.32)↑	0.96(0.94,0.99)↓	0.92(0.88,0.97)↓	0.86(0.84,0.88)↓
MXF VS. NO MXF	≤ 30 days	0.59(0.37,0.93)	0.97(0.15,6.24)	0.52(0.30,0.91)↓	0.76(0.33,1.77)	2.05(1.78,2.35)↑
	31 – 60 days	0.71(0.43,1.15)	0.00(0.00,0.00)	0.63(0.35,1.13)	0.93(0.39,2.25)	1.43(1.18,1.72)↑
	≥ 61 days	0.99(0.93,1.06)	1.02(0.69,1.51)	0.99(0.92,1.06)	1.10(0.95,1.27)	0.89(0.86,0.93)↓
FLQ VS. AMX	≤ 30 days	1.00(0.84,1.19)	1.49(0.69,3.19)	0.94(0.77,1.16)	1.08(0.77,1.50)	2.86(2.61,3.13)↑
	31 – 60 days	0.95(0.79,1.15)	0.07(0.04,0.12)↓	0.94(0.75,1.17)	0.92(0.65,1.31)	2.18(1.96,2.44)↑
	≥ 61 days	0.99(0.96,1.02)	1.14(0.94,1.40)	0.98(0.95,1.02)	1.03(0.96,1.11)	1.19(1.16,1.22)↑
FLQ VS. AZM	≤ 30 days	0.87(0.73,1.03)	1.14(0.54,2.39)	0.83(0.68,1.02)	0.98(0.70,1.37)	2.35(2.18,2.53)↑
	31 – 60 days	0.99(0.82,1.19)	0.06(0.04,0.09)↓	0.93(0.75,1.16)	1.06(0.75,1.49)	1.94(1.77,2.13)↑
	≥ 61 days	0.93(0.90,0.96)↓	1.10(0.91,1.34)	0.91(0.88,0.94)↓	1.00(0.93,1.08)	1.29(1.25,1.32)↑
FLQ VS. LEX	≤ 30 days	0.66(0.55,0.78)↓	0.68(0.32,1.42)	0.70(0.57,0.87)↓	0.47(0.34,0.66)↓	1.80(1.67,1.95)↑
	31 – 60 days	0.85(0.70,1.04)	0.05(0.03,0.09)↓	0.80(0.64,1.01)	0.99(0.68,1.44)	1.48(1.34,1.64)↑
	≥ 61 days	0.92(0.89,0.95)↓	1.13(0.92,1.40)	0.92(0.89,0.96)↓	0.86(0.80,0.93)↓	1.06(1.03,1.09)↑
FLQ VS. AMC	≤ 30 days	0.93(0.77,1.11)	1.05(0.48,2.32)	0.96(0.77,1.19)	0.72(0.51,1.02)	1.37(1.27,1.48)↑

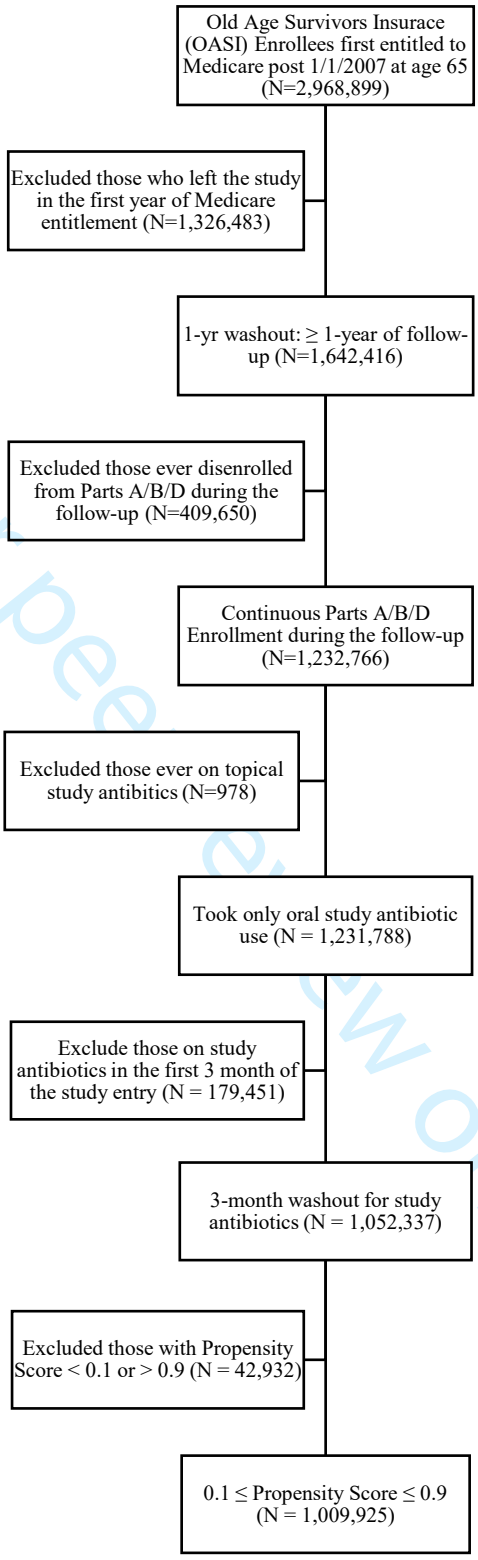
	31 – 60 days	0.94(0.77,1.15)	0.04(0.02,0.07) ↓	0.90(0.72,1.14)	1.24(0.83,1.86)	1.19(1.08,1.31) ↑
	≥ 61 days	0.93(0.90,0.97) ↓	1.19(0.95,1.49)	0.93(0.89,0.96) ↓	0.98(0.90,1.06)	1.06(1.03,1.09) ↑

Abbreviations: HR, hazard ratio, CI, confidence interval; FLQ, fluoroquinolone; CIP, ciprofloxacin; LVX, levofloxacin; MXF, moxifloxacin; AMX, Amoxicillin; AMC, Amoxicillin Clavulanate; AZT, Azithromycin; LEX, Cephalexin.
↑= significantly high with P-value < 0.001, ↑= significantly high with 0.001 ≤ P-value < 0.05
↓= significantly low with P-value < 0.001, ↓= significantly high with 0.001 ≤ P-value < 0.05

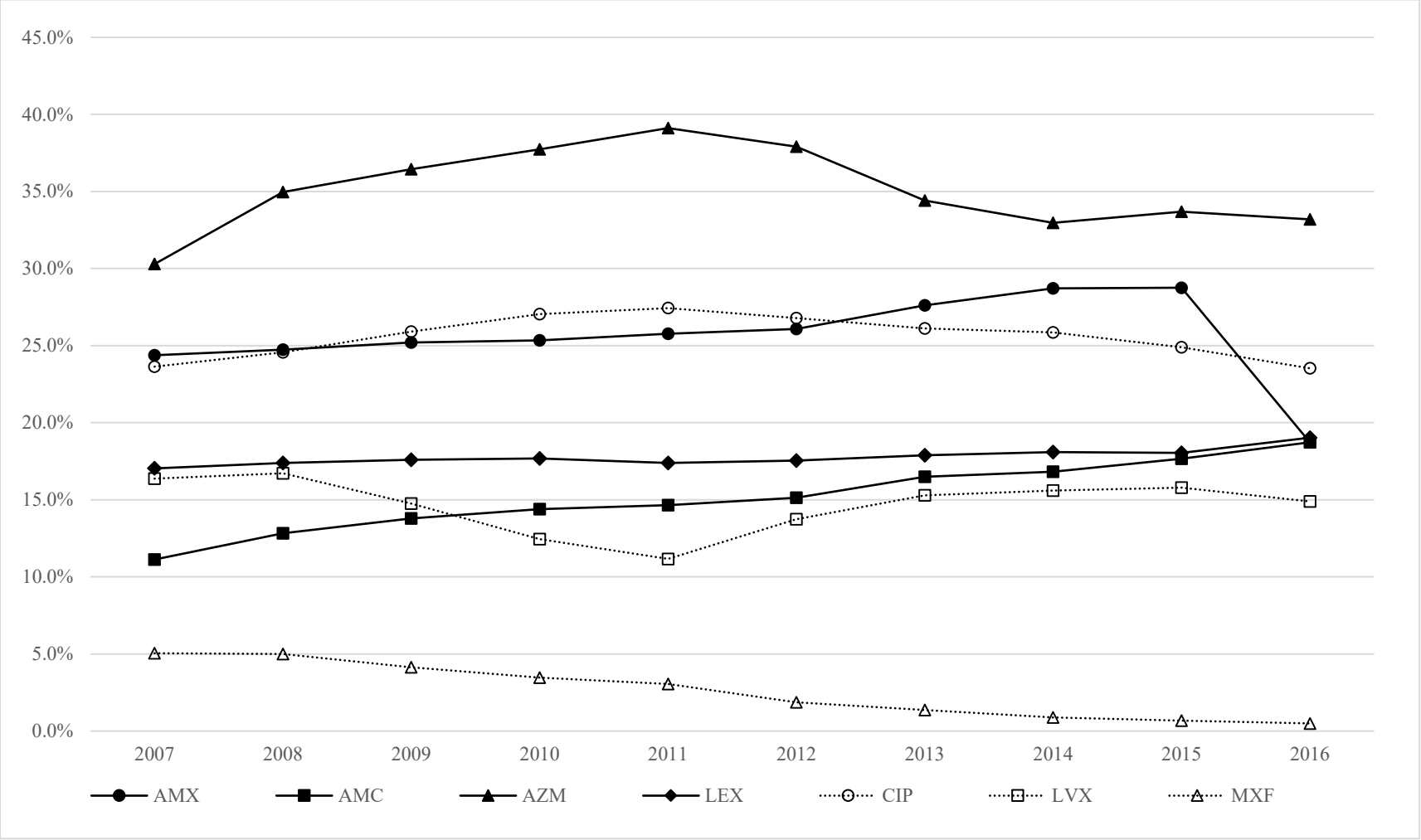
Table 4. Pairwise Comparisons

Comparison	Temporal Exposure	Any Tendon Rupture HR(95% CI)	Achilles Tendon Rupture HR(95% CI)	Complete Rupture of Rotator Cuff HR(95% CI)	Other Tendon Rupture HR(95% CI)	Death (Competing risk) HR(95% CI)
HRs comparing use of each FQ with use of each non-FQ antibiotics in a ≤30-day window						
CIP VS. LVX	**≤ 30 days**	0.84(0.75,0.94)↓	0.48(0.27,0.86) ↓	0.82(0.73,0.94) ↓	0.87(0.67,1.15)	0.67(0.63,0.71)↓↓
CIP VS. MXF	**≤ 30 days**	1.63(1.02,2.61)↑	1.08(0.16,7.29)	1.84(1.05,3.24)↑	1.10(0.47,2.60)	0.72(0.62,0.83)↓↓
LVX VS. MXF	**≤ 30 days**	1.95(1.21,3.13)↑	2.26(0.34,15.17)	2.24(1.27,3.94)↑	1.26(0.53,3.01)	1.07(0.93,1.24)
CIP VS. AMX	**≤ 30 days**	1.11(1.01,1.23)↑	1.20(0.66,2.16)	1.09(0.97,1.21)	1.06(0.84,1.34)	2.23(2.05,2.44)↑↑
CIP VS. AZM	**≤ 30 days**	0.97(0.87,1.06)	0.91(0.53,1.57)	0.96(0.86,1.07)	0.96(0.77,1.21)	1.84(1.71,1.97)↑↑
CIP VS. LEX	**≤ 30 days**	0.73(0.66,0.81)↓↓	0.55(0.31,0.95) ↓	0.81(0.72,0.91)↓↓	0.47(0.37,0.59)↑↑	1.41(1.31,1.52)↑↑
CIP VS. AMC	**≤ 30 days**	1.03(0.91,1.16)	0.84(0.46,1.56)	1.10(0.96,1.25)	0.71(0.56,0.92)↓	1.07(1.00,1.15)
LVX VS. AMX	**≤ 30 days**	1.33(1.19,1.49)↑↑	2.50(1.45,4.29)↑	1.32(1.16,1.49)↑↑	1.22(0.93,1.59)	3.34(3.07,3.64)↑↑
LVX VS. AZM	**≤ 30 days**	1.15(1.03,1.29)↑	1.91(1.13,3.23)↑	1.16(1.03,1.31)↑	1.10(0.84,1.44)	2.75(2.57,2.95)↑↑
LVX VS. LEX	**≤ 30 days**	0.87(0.78,0.98) ↓	1.14(0.68,1.92)	0.98(0.86,1.12)	0.54(0.41,0.69)↑↑	2.11(1.97,2.27)↑↑
LVX VS. AMC	**≤ 30 days**	1.23(1.08,1.40)↑	1.76(0.98,3.15)	1.33(1.15,1.54)↑↑	0.82(0.62,1.08)	1.60(1.49,1.72)↑↑
MXF VS. AMX	**≤ 30 days**	0.68(0.43,1.09)	1.10(0.16,7.41)	0.59(0.34,1.03)	0.96(0.41,2.27)	3.12(2.67,3.65)↑↑
MXF VS. AZM	**≤ 30 days**	0.59(0.37,0.94) ↓	0.84(0.13,5.65)	0.52(0.30,0.91)↓	0.88(0.37,2.07)	2.57(2.21,2.98)↑↑
MXF VS. LEX	**≤ 30 days**	0.45(0.28,0.72) ↓	0.50(0.08,3.35)	0.44(0.25,0.77)↓	0.43(0.18,1.00)	1.97(1.70,2.‡29)↑↑
MXF VS. AMC	**≤ 30 days**	0.63(0.39,1.01)	0.78(0.11,5.33)	0.60(0.34,1.05)	0.65(0.28,1.53)	1.50(1.29,1.73)↑↑
HRs comparing use of FQ as a class with use of each non-FQ antibiotics across different time window						
FLQ VS. AMX	**Overall**	0.98(0.90,1.07)	0.49(0.36,0.68)	0.95(0.86,1.06)	1.01(0.86,1.19)	1.95(1.86,2.05)↑↑
FLQ VS. AZM	**Overall**	0.93(0.85,1.01)	0.42(0.30,0.57)	0.89(0.80,0.98)↓	1.01(0.86,1.19)	1.80(1.73,1.88)↑↑
FLQ VS. LEX	**Overall**	0.80(0.73,0.88)	0.34(0.24,0.47)	0.80(0.72,0.89)	0.74(0.62,0.88)	1.42(1.35,1.48)↑↑
FLQ VS. AMC	**Overall**	0.93(0.85,1.02)	0.37(0.26,0.52)	0.93(0.83,1.03)	0.96(0.80,1.15)	1.20(1.15,1.25)↑↑

Abbreviations: HR, hazard ratio, CI, confidence interval; FLQ, fluoroquinolone; CIP, ciprofloxacin; LVX, levofloxacin; MXF, moxifloxacin; AMX, Amoxicillin; AMC, Amoxicillin Clavulanate; AZT, Azithromycin; LEX, Cephalexin.
↑↑= significantly high with P-value < 0.001, ↑= significantly high with 0.001 ≤ P-value < 0.05
↓↓= significantly low with P-value < 0.001, ↓= significantly high with 0.001 ≤ P-value < 0.05



Supplementary Figure. Secular Trend of Study Antibiotic Use



X-axis: Calendar year.

Y-axis: % of patients on each drug class.

STROBE Statement—Checklist of items that should be included in reports of ***case-control studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	6
		(*b*) For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	8-9
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-9
		(*b*) Describe any methods used to examine subgroups and interactions	n/a
		(*c*) Explain how missing data were addressed	n/a
		(*d*) If applicable, explain how matching of cases and controls was addressed	n/a
		(*e*) Describe any sensitivity analyses	n/a
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	9
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9-10
		(b) Indicate number of participants with missing data for each variable of interest	n/a
Outcome data	15*	Report numbers in each exposure category, or summary measures of exposure	10

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-14
		(*b*) Report category boundaries when continuous variables were categorized	12-13
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14-17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

*Give information separately for cases and controls.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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The association between Tendon Ruptures and Use of Fluoroquinolone, and other oral antibiotics: A 10-year Retrospective Study of 1 million U.S. senior Medicare beneficiaries

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The association between Tendon Ruptures and Use of Fluoroquinolone, and other oral antibiotics: A 10-year Retrospective Study of 1 million U.S. senior Medicare beneficiaries

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4000 Words (4000 Max)

Abstract (298 words; 300 Max)

Objectives: To assess the association of fluoroquinolone use with tendon ruptures compared to no fluoroquinolone and that of the four most commonly prescribed non-fluoroquinolone antibiotics in the US.

Design: Retrospective observational study.

Setting: U.S. seniors enrolled in the federal old-age, survivor's insurance program.

Participants: 1,009,925 Medicare fee-for-service beneficiaries and their inpatient, outpatient, prescription drug records were used.

Interventions: Seven oral antibiotics, fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin) and amoxicillin, amoxicillin-clavulanate, azithromycin and cephalexin.

Primary and Secondary Outcome measures: All tendon ruptures combined, and three types of tendon ruptures by anatomic site, Achilles tendon rupture, rupture of rotator cuff and other tendon ruptures occurred in 2007-2016.

Results: Of three fluoroquinolones, only levofloxacin exhibited a significant increased risk of tendon ruptures - 16% (HR=1.16; 95% CI 1.06-1.28), and 120% (HR=2.20; 95% CI 1.50-3.24) for rotator cuff and Achilles tendon rupture respectively in the ≤30-day window. Ciprofloxacin (HR=0.96; 95% CI 0.89-1.03) and moxifloxacin (HR=0.59; 95% CI 0.37-0.93) exhibited no increased risk of tendon ruptures combined.

Among the non-fluoroquinolone antibiotics, cephalexin exhibited *increased* risk of combined tendon ruptures (HR=1.31; 95% CI 1.22-1.41) and modest to large risks across all anatomic rupture sites (HRs 1.19-1.93) at ≤30-day window. Notably, the risk of

levofloxacin never exceeded the risk of the non-fluoroquinolone, cephalexin in any comparison.

Conclusions: In our study, fluoroquinolones as a class were not associated with the increased risk of tendon ruptures. Neither ciprofloxacin nor moxifloxacin exhibited any risk for tendon ruptures. Levofloxacin did exhibit significant increased risk. Cephalexin with no reported effect on metalloprotease activity had an equal or greater risk than levofloxacin; so we question whether metalloprotease activity has any relevance to observed associations with tendon rupture. Confounding by indication bias may be more relevant and should be given more consideration as explanation for significant associations in observational studies of tendon rupture.

Strengths and limitations of this study

- We conducted a large (more than 1 million US senior subjects) retrospective study of outpatient prescription drug records to assess the association between the use of fluoroquinolones and the occurrence of tendon ruptures compared to the most commonly used non-fluoroquinolone oral antibiotics.
- Our study included all oral fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin) prescribed in the US and the four most commonly prescribed non-fluoroquinolone antibiotics: amoxicillin, amoxicillin-clavulanate, azithromycin and cephalexin as controls.
- In addition to reporting the risk of any tendon rupture, we also reported the risk of three types of tendon ruptures by anatomic site 1) Achilles tendon rupture, 2) rupture of rotator cuff and 3) tendon ruptures on other anatomic sites as separate outcomes.
- This study is possibly only applicable to U.S. senior, aged 65 or more, Medicare fee-for-service beneficiaries.
- We had no options to verify claims diagnoses via chart review.

Introduction

Fluoroquinolones (FQ) are among the most widely prescribed antibiotics in the outpatient setting[1,2] due to their broad spectrum treatment of bacteria found in respiratory, urinary, joint, and skin infections. Several observational studies have reported the association between the use of FQs and tendinitis and tendon rupture (TR), especially of the Achilles tendon[3–12] and the U.S. Food and Drug Administration (FDA) issued black box warnings to FQ antibiotics beginning in 2008.[13] The warning was updated in 2016 to recommend using alternative antibiotics when possible.[14,15] The fact that FQs upregulate the production of metalloproteinase enzymes with collagenase activity that could weaken tendons is taken as a mechanism to explain this reported risk.[16–18]

Studies that reported association between FQ use and TR used one or more other antibiotics as controls. One study compared the FQ rupture rates with patients using azithromycin, the most frequently used oral antibiotic in the US. Only two focused principally on TR risk among the elderly. None compared TR rates of *FQs* with those of cephalexin -- the 3rd most commonly prescribed oral antibiotic in the US.

The Virtual Research Data Center (VRDC) of Center for Medicare and Medicaid Services (CMS)[19] carries more than 10 years of Medicare claims, which include information about the usage of prescription drugs and encounter diagnoses (including tendon ruptures). It also carries information about 42 major chronic conditions, demographic characteristic and vital status. We conducted a large observational study using the VRDC to assess the association of FQ antibiotics with TR compared to that of

the four most commonly prescribed non-FQ antibiotics in the US. Here we report the results of that analysis.

Methods

Patient and public involvement

Neither patients nor the public were not involved in the design of the study.

Study population

We derived our study population from a 20% random sample of Medicare prescription drug coverage (Part D) enrollees who first enrolled in the Medicare under old age and survivors insurance within a month of age 65 (779-781 month-old) and on or after 1/1/2007 - the first full year of Part D prescriptions availability. We included claim data through 12/31/2016, the end of VRDC claim data available to us. All of the VRDC data is de-identified and researchers must perform all of their analysis within the VRDC computer systems, and can only pull statistical results from it.[19] This study was declared not human subject research by the Office of Human Research Protection at the National Institutes of Health and by the CMS's Privacy Board.

We required subjects to be continuously enrolled in hospital insurance (Part A) and medical insurance (Part B) to assure we had full outpatient and inpatient claims data, which are not available for nearly 20% of subjects with Part D only.[20] To obtain a cohort of new TR patients, we excluded individuals with TRs recorded in the first year of their Medicare entitlement.[21] In order to assure sufficient follow-up, we excluded

individuals with less than 1-year follow-up. Moreover, to obtain incident (or new) drug user cohort, we excluded individuals who were prescribed any study antibiotics during their first 3-month after Part D enrollment, while ignoring the data during the same time window for individuals not taking study antibiotics. By doing so, we minimize survivor bias from a prevalent users (Figure 1 Consort Diagram).

Primary Outcome

We identified patients with TR based upon International Classification of Diseases (ICD)-9-CM codes of 726.13, 727.60-727.69, and ICD-10-CM codes of M66.2, M66.3, M66.8, M66.9, and M75.1. We combined all TRs and reported them as one outcome, and report three types of TRs by anatomic site 1) Achilles tendon rupture, 2) rupture of rotator cuff and 3) TRs on other anatomic sites as separate outcomes. We focused on Achilles TR because it was the sole focus of many prior studies and on rotator cuff TR because it is the predominant TR of the elderly. We lumped the remaining as "other TRs".

Study antibiotics

We included a total of seven study antibiotics prescribed in the US including all three oral FQs (moxifloxacin (MXF), ciprofloxacin (CIP), levofloxacin (LVX), the active stereoisomer of ofloxacin) and the four most frequently prescribed non-FQ oral antibiotics (amoxicillin (AMX), amoxicillin clavulanate (AMC), azithromycin (AZT) and cephalexin (LEX)) as a control. Ciprofloxacin and the four non-FQ, study antibiotics were the five most frequently used U.S. oral antibiotics in 2011.

Statistical Analysis

We analyzed each of the four TR outcomes in separate Fine-Gray competing risk regression analyses with death as the competing risk.[22,23] Individuals became eligible for "the study" at their Medicare enrollment but prescription data did not become available until their Part D enrollment. We followed them from their entry in Part D (while accounting for left truncation[24]) until their first diagnosis of TR, death, switch to a capitated plan, disenrollment from Medicare or 12/31/2016 – whichever came first. In each regression analysis, we included the seven antibiotics whose effects on TR were our primary interest. We adjusted hazard ratio (HR) of each study antibiotic for concurrent use of the other study antibiotics. We also adjusted for calendar year of individual's Part D entry, to account for secular trends, and their socio-demographic characteristics of gender, race, rural residency (Yes/No) and income status. We inferred individual's income level from the monthly indicators of dual-eligibility and Low Income Subsidy (LIS) status, which separate subjects into three groups; 1) dual whose income is below 135% Federal Poverty Line (FPL); 2) non-dual LIS whose income is between 135 and 150% FPL; and 3) non-dual no LIS whose income is above 150% FPL, respectively. We used this variable in the analysis as a surrogate for economic status.[25] We also included the 42 chronic conditions within the Medicare Master Beneficiary Summary File [26] that had >1% prevalence as measures of overall health. We assumed that patients were on a given study drug from the prescription dispensing date to the end of days of supply. We did not distinguish between different brands of a study drugs. Following the approach of prior studies,[3–5] we separated subjects by temporal exposure within each study drug,

including groups for never exposed, exposed within 30 days, 31-60 days, and >60 days of the index (or TR event) time. Thus, by this approach we could detect the presumed short term action of the FQ's on tendons and avoid the risk of non-differential misclassification that can occur with too simple (yes/no) drug exposure measures.[27] In order to minimize the immortal time bias, we treated all drug usage measures and all socio-demographic characteristics, except gender, race and rural residency, as time-varying covariates.[28,29] In order to mitigate selection bias toward use of any study antibiotics, we employed a propensity score (PS) approach.[30,31] We first derived a PS of taking any of study antibiotics as a function of individual's characteristics at the time of the first antibiotic use after Part D entry from a multiple logistic regression. We used the median days to the first study antibiotic use in patients taking study antibiotics as the cutoff time for individuals not taking study antibiotics. We performed our analyses with an inverse propensity score weight (IPSW) excluding individuals with the PS below 0.1 and above 0.9, to mitigate poorer performance in the presence of a strong treatment-selection process.[32] In post-hoc analyses, we also compared the risk of TR of each study antibiotics to that of every other study antibiotic on a pairwise basis.

Results

Study population and Secular trend

From our 20% sample of Part D enrollees, 1,009,925 individuals satisfied all our selection criteria including the washout of individuals with any antibiotic use in their first 3-month of Part D enrollment (Figure 1 Consort Diagram). Follow-up began with an individual's enrollment in Part D program (median (IQR) 0 (0-122) days from the

Medicare entitlement). We followed them for a median of 3.6 years (total 4,030,897 patient-years) until their first diagnosis of TR (3.5%), death (4.6%), switch to a capitated plan (12.6%), disenrollment from Medicare (<1%) or study end on 12/31/2016 (79.3%), whichever came first. Patients had their first post enrollment claim with a diagnosis of TR at a median age of 68.5 (IQR 67.2-70.4). The proportions of non-Hispanic White, female and rural residents were 80.7%, 57.0%, and 22.6% respectively. About a fifth of individuals received federal/state subsidies, i.e. Medicaid coverage on top of Medicare (dual 16.1%) or assistance in paying their Part D premium and coinsurance/copayment (non-dual LIS 2.7%). Among the 42 Medicare chronic conditions, hypertension (67.3%), hyperlipidemia (68.4%), cataract (46.4%), rheumatoid arthritis/osteoarthritis (36.6%), anemia (30.4%), ischemic heart disease (26.2%), and chronic kidney disease (17.9%) were the seven most prevalent (Table 1).

Of the 328,654 (33.0%) patients who ever took an FQ, 71.5%, 47.5% and 4.5% had taken CIP, LVX and MXF respectively. Of 576,885 (57.1%) of patients who ever took a non-FQ antibiotic, the figures were 53.6%, 44.9%, 33.9% and 31.1% for AZM, AMX, LEX, and AMC, respectively. Patients who took one or more study antibiotics took a median (IQR) of 3.0 (1.0-6.0) study antibiotic prescriptions and took a median (IQR) 2.0 (1.0-3.0) different study antibiotics during the observation period. About 2.5% patients who took one or more study antibiotics took one or more such antibiotics at the same time. Secular trends in study antibiotics usage existed (Supplementary Figure 1). MXF usage declined precipitously from 5.0% in 2007 to almost zero in 2016 – overweighting the MXF statistics for early entrants into Medicare and yielding a longer mean follow-up

time. CIP use hit a peak, and LVX, a nadir, in 2011. The use of AMX, AMC and LEX trended slowly upward (Supplementary Figure 1). The mode (median) of supply durations for each antibiotics were short--10 (7) for AMX, 10 (10) for AMC, 5 (5) for AZM, 10 (7) for LEX, 7 (7) for CIP, 10 (7) for LVX, 10 (11) for MXF. About 35% of individuals were never exposed to any of the study antibiotics during the study period.

Unadjusted figures for TR prevalence across each of the seven study antibiotic users and the no study antibiotic users ranged from a high of 5.2% for MXF to a low of 2.9% for no antibiotic (Table 1). Except for MXF, the *unadjusted* prevalence of TRs associated with each non-FQ antibiotic was *greater than* or equal to that of each FQ antibiotic. The TR rates per 1000 patient-years followed the same pattern, with the non-FQ antibiotics topping the rates of all FQs except MXF (with the highest rate), possibly due to overweighting of MXF usage in the early years of the study. Patients who ever took an FQ had the highest unadjusted rate of death per 1000 person-years. LVX's death rate was nearly twice the rate of each non-FQ antibiotics. The size of the associations with conditions like diabetes, chronic renal failure and heart failure paralleled the magnitude of the death rates and was generally higher with FQs than non-FQ antibiotics (Table 1).

Primary Analysis

Table 2 presents HRs for all non-antibiotic covariates in our Fine-Gray competing risk regression with IPSW. For simplicity sake, in Table 2, we report the HRs of all anatomic types of tendon ruptures taken together. Being a female (vs. male), African-American, Hispanic, and Asian (vs. white), being dual or non-dual LIS (vs. non-dual no LIS) and

living in a rural area were all associated with a *reduced* risk of tendon rupture. These risk reductions were 24% or more for all but Hispanics and rural residency covariates, and the reductions were similar across all anatomic sites. In general, life-threatening chronic conditions, such as AMI, COPD, heart failure and colorectal/lung/endometrial cancers were associated with a lower risk of TR in a range of 15-60% below control possibly due to constrained physical activity and/or shortened life span. Notably, diabetes and chronic renal disease, previously reported as risk factors for TR,[33,34] exhibited no increased TR risk. Mobility impairments had reduced risk of TR similar to that of the severe life-threatening conditions, likely due to reduced activity. Most conditions with low life threats such as cataract, glaucoma, depression, asthma, hyperlipidemia, hypertension, prostatic hyperplasia, migraine/other chronic headache, and deafness/hearing impairment exhibited risks of 8 to 34% *above* controls probably for reasons related to longer life spans and less inhibited activity. Ischemic heart did not fit the mold of sicker equals lower TR risk. Patients with rheumatoid arthritis/osteoarthritis were a special case and had TR risk of 184% *above* control possibly due to joint and associated tendon inflammation with these disorders. Fibromyalgia/chronic pain and fatigue also exhibited a 39% increased risk of TR possibly also due to an inflammatory component.

The Achilles tendon carries the full force of the extra weight carried by obese patients and obesity was associated with a significant (13%) increase in Achilles TR ruptures while its effect on other TR classes was significant but miniscule (2-3%) (Data not shown).

Effect of antibiotics

We report HRs from our primary analysis in tables separate from the non-antibiotic covariates. Table 3 shows the risk associated with each study antibiotic broken down by time lag between the antibiotic use and the TRs (separate rows), and by all TRs together and separately by anatomic sites (in columns). We also report HRs of death (competing risk). We used multiplicity corrected p-values to simultaneously test the difference of pairs of antibiotics to minimize the chance of finding statistically significant difference by random chance.[35] Of the total 34,880 patients with any TR occurrence, complete rupture of rotator cuff represented the major share (80.5%), followed by other TRs (16.9%) and Achilles TR (2.6%). In the survival analysis, we followed patients until the first occurrence of TR; so, these figures count only the first TR occurrence independent of anatomic site.

Of the non-FQ antibiotics, AMX exhibited a reduced risk of TR compared to no AMX in every tendon class and time window, similar to its low risk in previous studies. It exhibited a significantly lower risk in the ≤30-day window except for the Achilles tendon. AZM and AMC exhibited a similar benign risk in all time windows except for TR of rotator cuff in >60-day window. LEX was the surprise non-FQ antibiotic. It exhibited modest to large *increase*d TR risk at ≤30-day window across all sites ranging from a low of 19% increase for complete rupture of rotator cuff to a high 93% increase for Achilles TR. Its risk was also significantly higher at ≤30-day window for all TRs taken together.

Of the FQs, CIP and MXF, the most and least frequently prescribed FQ, exhibited little to no increased risk of TR within each anatomic site and each time frame. LVX is the only FQ to exhibit a significant *increase* in TR risk - of 16%, and 120% for rupture of rotator

cuff and Achilles TR respectively in the ≤30-day window. Notably, the risk of LVX never exceeded the risk of the non-FQ, LEX in any comparison.

In a post-hoc analysis (Table 4), we compared the TR risk of each antibiotic with every other antibiotic (pairwise comparisons of FQ vs. FQ and FQ vs. non-FQ), for ≤30-day window and FQs as a class vs. each non-FQ after combining the data from the three time windows. These results paralleled the above-mentioned risk for each study antibiotic in Table 3. Again, TR risk for LVX was greater than that of CIP, MXF, AMC, AMX, and AZM in a ≤30-day window. However, LVX risk was comparable to that of LEX for Achilles TR, and rupture of rotator cuff and significantly lower than LEX for the other TR classes. When comparing the risk of FQs as a class against that of non-FQ antibiotics, most of the non-FQ antibiotics had significantly greater risk than the FQ class as a whole across all TR sites (See last 4 rows of Table 4).

In another analysis evaluating risk of death for each antibiotics, each FQ antibiotic exhibited a significant increase in death risk of – 46% (for CIP), 105% (for MXF) and 119% (for LVX) in a ≤30-day window. Among non-FQ antibiotics, only AMC exhibited 37% increased risk of death in a ≤30-day window. Overall, risk of death for FQs as a class far outweighed that of each non-FQ antibiotics.

Discussion

Our results conflict with the common assertion that the Achilles tendon rupture is the most common tendon rupture (up to 90% in one report[36]). In our elderly cohort, Achilles TRs were a tiny, 2.6%, of all TRs. Some of this difference may be explained by

the differences in demographics. Reports of high prevalence of Achilles TR came from studies of young military populations.[37,38] In contrast, our data came from an elderly Medicare population. Some of the difference could also be due to less ability to diagnose non-Achilles tendon ruptures until MRI joint imaging became widely available, because such TRs are less amenable to diagnosis by physical exam.

Many authorities describe the relationship between FQs and TRs as a class "effect". However, FQs as a class had no significant risk of TR compared with each of the four non-FQ antibiotics in any time window. CIP (n=234,994 subjects) is the oral FQ with the greatest use and with a greater effect on metalloproteases than other FQs.[39–41] However, neither MXF (n= 14,728 subjects) nor CIP had any TR risk at any anatomic site in any time window. CIP's lack of risk is consistent with two studies[5,9] in which CIP exhibited zero risk or small risks compared to ofloxacin, a racemic mixture whose active ingredient is the levo-isomer, LVX. We do see a strong association between LVX and TRs whether we used no LVX or three of the non-FQ antibiotics as controls. However, when we used LEX, a cephalosporin, as the control for LVX's effect on TRs, we saw no increased risk.

As noted in the introduction, the FDA has added a black box warning about tendon ruptures to the labels of fluoroquinolones. A 2015 paper[42] described the evidence for this decision based on the FDA's Adverse Event Reporting System (FAERS) database and an empirical Bayes geometric mean (EBGM) score, which is based on the relative frequency of spontaneous report about a given adverse event in one drug versus the

reporting of that adverse event across all drugs. This EBGM score based upon FAERS database has been useful but FAERS database is still limited by a lack of true denominator for population at risk, underreporting due to a voluntary reporting scheme and bias due to limited adjustment variables.[43] Our study was based on a well-defined Medicare population with 80 variable adjustments. The fact that levofloxacin's EBGM score was six times that of ofloxacin[42] though both drugs have the same active ingredient (the levo-isomer of ofloxacin) and the same dose of that ingredient, raises questions about what factors influenced that score.

One previous study described the effect of FQs on TR risk as small and unimportant.[10] Two studies reported no effect of FQs on TR risk.[9,11] At least 7 observational studies reported that the use of FQs increased risks of TR.[3–8,12] However, in all but one study, the number of TRs among patients taking an FQs was small (between 5 and 111). In comparison, our study included 12,517 (3.8%) such patients. One previous study did report a large number of TR events, 23,000 (3.5%) patients while on FQs and, like our study, it focused exclusively on elderly patients.[3] However, it did not compare the population of FQ users against non-users but FQ usage periods against non-usage periods in the same set of patients, which were likely periods without visits and thus could not account for the effect of increased clinical attention provided at visits requiring a strong systemic antibiotic. Furthermore, they assessed the association between AMX and TRs in separate analysis and used the risk of TRs in that analysis as the comparator for the risk observed in the FQ analysis. Finally, their analysis did not include death as a competing

risk as is recommend when death rates exceed event rates[23] which was likely the case because in the demographics of their study was very similar to ours.

In our study, AMX treated patients exhibited a similar absolute risk of TR as to LVX treated patients (7.56 vs. 7.47 per 1000 patient-years). However, they had fewer comorbidities (as in Daneman's study), almost 14% fewer hospitalizations and half of death rate, compared to patients taking LVX (7.56 vs. 18.50 per 1000 patient-years). So the two populations are not comparable. LVX exhibited 119% increased risk of death in a ≤30-day window. They appears to be reserved for more severe infections or more fragile patients and thus subject to differential biases.

The reported activation of metalloprotease activity by FQs has underpinned the idea of a causal link between FQs and TRs. The argument goes as follows: FQs stimulate metalloproteases, which can break down collagen; the tendon is made of collagen; so FQs may cause TRs. However, our data disrupts this argument. CIP which strongly *stimulates* metalloprotease activity,[17,18] exhibited *no* risk of TRs in our study, and LEX which *inhibits* metalloprotease activity[44,45] exhibited a *large* risk. So we have to question whether metalloprotease activity has any relevance to TR risk, and consider other explanations for the observed associations.

The indication for an antibiotic is a presumed bacterial infection. The reported associations between antibiotics and TR could be a consequence of the indication (infection) rather than the antibiotic use to treat it. It could be a perfects example of the

confounding by indication.[46] Such a bias could explain many reported associations between drugs and TR risk including associations with non-antibiotic drugs reported by Nyyssönen.[8]

This indication (and infection) bias could generate an association between the antibiotic and TRs in different ways. First, the bacterial infection might directly increase the risk of TR via stimulation of general immune or cytokine responses, or even by direct bacterial invasion. A recent study found gram-positive bacteria in a major share of ruptured tendons but not in "control" tendons removed surgically for grafting,[47] So the possibility of direct invasion of tendons by circulating bacteria with subsequent weakening and rupture is plausible.

Secondly, the greater clinical attention likely focused on patients needing systemic antibiotics, especially those with more severe infections, could increase the chance of noticing and documenting a pre-existing TR. A reservoir of not-yet-diagnosed such cases is likely to exist, because patients do not necessarily correctly identify joint and extremity symptoms as TRs and seek immediate care for them. Tendon ruptures of the shoulder capsule, for example, are notorious for developing symptoms slowly over 2-3 years[48] before being correctly diagnosed. Even Achilles tendon ruptures, can be missed (in 30% of cases) at the first presentation.[49] Seeger et al. reviewed the medical records of patients with an insurance claim reporting TRs following antibiotic use and found that nearly half of the TRs recorded in the claims were either something else (e.g., Bursa

inflammation miscoded as a TR) or had occurred pre antibiotic use but only seen in a claim post antibiotic use.[11]

Indication bias is a plausible explanations for associations reported in observational studies and it should be considered more often before assuming the associations are causal.

Limitation

This study faces all of the limitations of observational studies. Furthermore, it applies only to fee-for-service Medicare populations. In addition, we had no options to verify claims diagnoses via chart review. From a statistical point of view, our findings may have some limitations. First, we included 80 covariates in one analysis and concern about intercorrelation affecting the validity could exist. To evaluate the intercorrelation, we calculated an 80x80 correlation matrix of estimated regression which can deliver information about the strength of intercorrelation and indicate the existence of a collinear relationship between two predictors. All pairwise correlations (except diagonal elements) were below 0.5, and the largest was 0.33 indicating minimal bias due to intercorrelation. We also did not consider interactions among covariates in our main analysis because of the problem of overfitting. We ran 4 sensitivity analyses with interaction terms between the study medications and 4 covariates (rheumatoid arthritis/osteoarthritis, obesity, female sex, lung cancer). The inclusion of interactions did not change our conclusion of no TR risk for FQ as a class.

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Competing interests Statement

All authors have no competing interest to declare.

Contributorship Statement

SB: study conception, design, analysis and interpretation; critical review of study content; manuscript drafting; approval of the final manuscript. JL: study concept and interpretation; manuscript drafting; approval of the final manuscript. VH: study interpretation; manuscript drafting; approval of the final manuscript. CJM: study conception, design and interpretation; critical review of study content; manuscript drafting; approval of the final manuscript.

Data availability

The authors confirm that the data supporting the findings of this study are available within the article [and/or] its supplementary materials.

Patient Consent for publication: Not required.

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Figure 1. Consort Diagram

Table 1. Outcome, Medical/Medication Use, Diseases and Patient Characteristics by Type of Antibiotics

Variable	Overall	FLQ	CIP	LVX	MXF	AMX	AZM	LEX	AMC	None
N	1,009,925	328,654	234,994	155,991	14,728	259,125	308,985	195,731	179,616	356,364
Tendon Rupture	34,880(3.5)	12,517(3.8)	8,811(3.7)	5,904(3.8)	770(5.2)	9,636(3.7)	12,448(4.0)	8,019(4.1)	6,622(3.7)	10,169(2.9)
Death	46,468(4.6)	23,249(7.1)	14,821(6.3)	14,610(9.4)	2,136(14.5)	9,632(3.7)	14,608(4.7)	11,394(5.8)	9,951(5.5)	13,645(3.8)
Censored at HMO entry	127,162(12.6)	27,573(8.4)	19,847(8.4)	11,142(7.1)	1,571(10.7)	21,215(8.2)	26,140(8.5)	14,887(7.6)	12,674(7.1)	65,886(18.5)
Censored at disenrollment	145(0.0)	25(0.0)	13(0.0)	13(0.0)	2(0.0)	19(0.0)	27(0.0)	23(0.0)	16(0.0)	85(0.0)
Censored at Dec 31 2016	801,270(79.3)	265,290(80.7)	191,502(81.5)	124,322(79.7)	10,249(69.6)	218,623(84.4)	255,762(82.8)	161,408(82.5)	150,353(83.7)	266,579(74.8)
Years of follow-up, median(total)	3.6(4,030,897)	4.6(1,620,894)	4.8(1,190,308)	4.8(789,849)	6.0(87,397)	4.5(1,274,357)	4.6(1,529,370)	4.8(1,000,459)	4.6(890,340)	2.5(1,067,731)
Tendon rupture, 1000 person-years	8.65	7.72	7.40	7.47	8.81	7.56	8.14	8.02	7.44	9.52
Death, 1000 person-years	11.53	14.34	12.45	18.50	24.44	7.56	9.55	11.39	11.18	12.78
Female	575,885(57.0)	197,915(60.2)	146,745(62.4)	89,682(57.5)	8,747(59.4)	151,383(58.4)	194,101(62.8)	113,308(57.9)	104,749(58.3)	191,069(53.6)
White	814,933(80.7)	274,785(83.6)	196,048(83.4)	131,725(84.4)	12,464(84.6)	215,101(83.0)	259,657(84.0)	167,825(85.7)	153,723(85.6)	271,906(76.3)
Black	75,930(7.5)	20,017(6.1)	14,286(6.1)	8,893(5.7)	956(6.5)	15,622(6.0)	17,296(5.6)	9,625(4.9)	9,199(5.1)	35,023(9.8)
Hispanic	56,582(5.6)	17,044(5.2)	12,607(5.4)	7,943(5.1)	628(4.3)	12,494(4.8)	14,805(4.8)	8,976(4.6)	7,802(4.3)	24,391(6.8)
Asian	26,336(2.6)	7,316(2.2)	5,362(2.3)	3,144(2.0)	356(2.4)	7,624(2.9)	7,945(2.6)	3,539(1.8)	3,440(1.9)	10,437(2.9)
Other	36,144(3.6)	9,492(2.9)	6,691(2.8)	4,286(2.7)	324(2.2)	8,284(3.2)	9,282(3.0)	5,766(2.9)	5,452(3.0)	14,607(4.1)
Ever Dual	162,988(16.1)	54,055(16.4)	38,277(16.3)	28,156(18.0)	2,908(19.7)	35,305(13.6)	44,940(14.5)	30,962(15.8)	25,255(14.1)	66,986(18.8)
Non-Dual LIS	26,955(2.7)	7,648(2.3)	5,459(2.3)	3,746(2.4)	385(2.6)	5,224(2.0)	6,828(2.2)	4,191(2.1)	3,818(2.1)	12,595(3.5)
Non-Dual No LIS	819,982(81.2)	266,951(81.2)	191,258(81.4)	124,089(79.5)	11,435(77.6)	218,596(84.4)	257,217(83.2)	160,578(82.0)	150,543(83.8)	276,783(77.7)
Living in rural area	228,199(22.6)	78,581(23.9)	56,385(24.0)	38,847(24.9)	2,801(19.0)	58,805(22.7)	72,282(23.4)	49,977(25.5)	42,288(23.5)	77,087(21.6)
Days on Rx, median (IQR)	N/A	N/A	10.0(7.0-20.0)	10.0(7.0-17.0)	10.0(7.0-12.0)	10.0(7.0-20.0)	5.0(5.0-11.0)	10.0(7.0-16.0)	10.0(10.0-20.0)	N/A
Hospitalization	349,959(29.5)	198,846(45.4)	142,538(45.3)	113,829(52.5)	14,002(60.3)	132,304(38.8)	156,185(37.9)	119,209(45.9)	103,515(42.5)	51,525(14.4)
Outpatient visits per year, median (IQR)	19.6(11.1-33.0)	27.1(17.2-42.7)	27.3(17.5-42.9)	30.1(19.0-47.8)	34.0(21.7-53.7)	23.6(14.5-37.5)	24.6(15.5-38.8)	27.5(17.2-43.2)	26.6(16.7-42.2)	12.3(6.0-21.8)
AMI	21,222(2.1)	9,999(3.0)	6,810(2.9)	5,862(3.8)	698(4.7)	6,474(2.5)	8,079(2.6)	6,215(3.2)	5,292(2.9)	5,012(1.4)
Atrial Fibrillation	71,635(7.1)	31,752(9.7)	21,757(9.3)	17,731(11.4)	2,028(13.8)	23,974(9.3)	26,182(8.5)	21,935(11.2)	18,764(10.4)	16,314(4.6)
Cataract	468,608(46.4)	183,870(55.9)	134,196(57.1)	88,574(56.8)	9,216(62.6)	144,455(55.7)	174,897(56.6)	112,020(57.2)	101,079(56.3)	124,931(35.1)
Chronic Kidney Disease	180,441(17.9)	86,021(26.2)	62,323(26.5)	46,121(29.6)	4,651(31.6)	53,713(20.7)	65,577(21.2)	50,361(25.7)	43,182(24.0)	42,916(12.0)
COPD	130,840(13.0)	71,913(21.9)	43,961(18.7)	48,430(31.0)	6,106(41.5)	40,109(15.5)	66,536(21.5)	37,413(19.1)	37,579(20.9)	22,739(6.4)
Heart Failure	103,010(10.2)	51,814(15.8)	34,870(14.8)	31,377(20.1)	3,776(25.6)	32,792(12.7)	41,647(13.5)	31,585(16.1)	27,223(15.2)	21,907(6.1)
Diabetes	284,919(28.2)	113,424(34.5)	81,175(34.5)	57,697(37.0)	5,942(40.3)	81,155(31.3)	98,176(31.8)	67,548(34.5)	59,984(33.4)	81,448(22.9)
Glaucoma	150,839(14.9)	56,990(17.3)	41,984(17.9)	26,603(17.1)	2,930(19.9)	45,597(17.6)	54,726(17.7)	33,936(17.3)	31,065(17.3)	42,355(11.9)
Hip/Pelvic Fracture	7,982(0.8)	4,086(1.2)	3,000(1.3)	2,289(1.5)	274(1.9)	2,673(1.0)	3,005(1.0)	2,515(1.3)	1,914(1.1)	1,689(0.5)
Ischemic Heart Disease	264,648(26.2)	117,416(35.7)	82,182(35.0)	63,659(40.8)	6,956(47.2)	83,682(32.3)	101,999(33.0)	70,612(36.1)	63,363(35.3)	63,372(17.8)
Depression	210,714(20.9)	94,554(28.8)	68,625(29.2)	49,277(31.6)	5,298(36.0)	65,642(25.3)	83,253(26.9)	56,747(29.0)	51,150(28.5)	49,320(13.8)
Alzheimer's Disease or Senile Dementia	39,132(3.9)	19,796(6.0)	14,309(6.1)	11,030(7.1)	1,206(8.2)	11,140(4.3)	13,809(4.5)	11,846(6.1)	9,309(5.2)	9,400(2.6)
Osteoporosis	106,966(10.6)	47,033(14.3)	35,217(15.0)	22,918(14.7)	2,738(18.6)	34,610(13.4)	44,016(14.2)	26,996(13.8)	24,393(13.6)	25,216(7.1)

Rheumatoid Arthritis/Osteoarthritis	369,584(36.6)	160,091(48.7)	117,018(49.8)	80,115(51.4)	8,259(56.1)	126,702(48.9)	148,653(48.1)	101,310(51.8)	88,017(49.0)	81,855(23.0)
Stroke/Transient Ischemic Attack	58,886(5.8)	27,702(8.4)	19,843(8.4)	15,051(9.6)	1,670(11.3)	17,829(6.9)	22,038(7.1)	16,684(8.5)	14,245(7.9)	14,262(4.0)
Breast Cancer	45,316(4.5)	19,362(5.9)	14,344(6.1)	9,442(6.1)	984(6.7)	13,451(5.2)	17,676(5.7)	12,543(6.4)	10,156(5.7)	11,042(3.1)
Colorectal Cancer	15,905(1.6)	7,487(2.3)	5,421(2.3)	4,048(2.6)	390(2.6)	4,304(1.7)	5,170(1.7)	4,085(2.1)	3,605(2.0)	4,104(1.2)
Prostate Cancer	37,038(3.7)	19,705(6.0)	15,577(6.6)	9,232(5.9)	643(4.4)	10,967(4.2)	11,733(3.8)	9,252(4.7)	8,070(4.5)	8,333(2.3)
Lung Cancer	14,946(1.5)	8,965(2.7)	5,144(2.2)	6,356(4.1)	905(6.1)	3,859(1.5)	6,633(2.1)	3,977(2.0)	4,267(2.4)	2,733(0.8)
Endometrial Cancer	7,396(0.7)	3,447(1.0)	2,670(1.1)	1,635(1.0)	160(1.1)	2,095(0.8)	2,637(0.9)	1,957(1.0)	1,604(0.9)	1,847(0.5)
Anemia	307,310(30.4)	140,606(42.8)	100,819(42.9)	74,308(47.6)	7,980(54.2)	99,190(38.3)	118,327(38.3)	81,967(41.9)	72,587(40.4)	71,098(20.0)
Asthma	86,120(8.5)	46,350(14.1)	29,327(12.5)	30,152(19.3)	4,091(27.8)	27,632(10.7)	46,823(15.2)	24,426(12.5)	25,465(14.2)	13,802(3.9)
Hyperlipidemia	691,148(68.4)	257,086(78.2)	185,199(78.8)	123,828(79.4)	12,162(82.6)	199,236(76.9)	239,414(77.5)	152,879(78.1)	140,364(78.1)	201,258(56.5)
Hyperplasia	122,010(12.1)	59,809(18.2)	45,517(19.4)	28,616(18.3)	2,587(17.6)	39,031(15.1)	42,070(13.6)	31,606(16.1)	28,398(15.8)	27,336(7.7)
Hypertension	679,287(67.3)	253,601(77.2)	181,231(77.1)	124,646(79.9)	12,218(83.0)	192,686(74.4)	230,409(74.6)	150,995(77.1)	136,292(75.9)	201,777(56.6)
Hypothyroidism	197,447(19.6)	81,468(24.8)	59,450(25.3)	40,372(25.9)	4,198(28.5)	59,893(23.1)	76,582(24.8)	47,973(24.5)	44,249(24.6)	50,280(14.1)
Anxiety Disorders	148,983(14.8)	70,688(21.5)	51,377(21.9)	37,563(24.1)	4,032(27.4)	48,859(18.9)	62,418(20.2)	41,655(21.3)	37,588(20.9)	31,709(8.9)
Bipolar Disorder	17,882(1.8)	8,368(2.5)	6,104(2.6)	4,533(2.9)	468(3.2)	5,442(2.1)	6,658(2.2)	5,147(2.6)	4,227(2.4)	4,242(1.2)
Major Depressive Affective Disorder	153,182(15.2)	71,732(21.8)	52,101(22.2)	38,055(24.4)	4,148(28.2)	48,846(18.9)	61,872(20.0)	43,416(22.2)	38,642(21.5)	33,660(9.4)
Schizophrenia and other Psychotic Disorders	16,764(1.7)	8,591(2.6)	6,176(2.6)	4,934(3.2)	548(3.7)	4,421(1.7)	5,597(1.8)	5,101(2.6)	3,811(2.1)	4,300(1.2)
Epilepsy	16,155(1.6)	7,543(2.3)	5,383(2.3)	4,269(2.7)	415(2.8)	4,310(1.7)	5,488(1.8)	4,510(2.3)	3,621(2.0)	4,191(1.2)
Fibromyalgia, Chronic Pain and Fatigue	166,279(16.5)	78,877(24.0)	57,494(24.5)	41,843(26.8)	4,410(29.9)	56,152(21.7)	70,667(22.9)	48,422(24.7)	43,379(24.2)	33,843(9.5)
Viral Hepatitis (General)	11,969(1.2)	4,659(1.4)	3,188(1.4)	2,523(1.6)	287(1.9)	3,156(1.2)	3,732(1.2)	2,712(1.4)	2,348(1.3)	3,735(1.0)
Liver Disease Cirrhosis and other Liver Conditions	62,675(6.2)	31,930(9.7)	23,284(9.9)	17,386(11.1)	1,919(13.0)	19,624(7.6)	24,544(7.9)	17,393(8.9)	15,958(8.9)	13,350(3.7)
Leukemias and Lymphomas	13,906(1.4)	7,228(2.2)	4,822(2.1)	4,536(2.9)	551(3.7)	4,385(1.7)	5,905(1.9)	4,025(2.1)	3,969(2.2)	2,758(0.8)
Migraine and other Chronic Headache	31,628(3.1)	14,936(4.5)	11,282(4.8)	7,520(4.8)	873(5.9)	10,841(4.2)	13,893(4.5)	8,763(4.5)	8,403(4.7)	6,419(1.8)
Mobility Impairments	20,600(2.0)	10,182(3.1)	7,356(3.1)	5,767(3.7)	577(3.9)	5,372(2.1)	6,629(2.1)	5,995(3.1)	4,610(2.6)	5,439(1.5)
Obesity	185,101(18.3)	79,130(24.1)	56,609(24.1)	41,226(26.4)	3,997(27.1)	58,654(22.6)	69,611(22.5)	49,984(25.5)	43,740(24.4)	44,772(12.6)
Peripheral Vascular Disease	90,132(8.9)	45,276(13.8)	31,866(13.6)	25,977(16.7)	3,001(20.4)	28,747(11.1)	36,241(11.7)	28,343(14.5)	23,977(13.3)	18,446(5.2)
Tobacco Use Disorders	101,890(10.1)	45,304(13.8)	28,907(12.3)	27,202(17.4)	3,042(20.7)	27,261(10.5)	37,860(12.3)	25,002(12.8)	22,975(12.8)	26,896(7.5)
Pressure Ulcers and Chronic Ulcers	30,345(3.0)	17,688(5.4)	12,800(5.4)	10,603(6.8)	1,196(8.1)	9,006(3.5)	10,926(3.5)	13,404(6.8)	9,960(5.5)	4,992(1.4)
Deafness and Hearing Impairment	59,576(5.9)	27,383(8.3)	19,976(8.5)	14,014(9.0)	1,609(10.9)	21,213(8.2)	25,498(8.3)	16,849(8.6)	16,787(9.3)	11,900(3.3)

Note. Data are presented as No. (%) of patients unless otherwise noted.
Abbreviations: FLQ, fluoroquinolone; CIP, ciprofloxacin; LVX, levofloxacin; MXF, moxifloxacin; AMX, Amoxicillin; AMC, Amoxicillin Clavulanate; AZT, Azithromycin; LEX, Cephalexin; IQR, interquartile range.

Table 2. Hazard Ratios of Tendon Rupture for Each Covariate

Variables	Reference	HR(95% CI)
Female	Male	0.70(0.69,0.72)↓
Black	White	0.76(0.73,0.78)↓
Hispanic		0.91(0.87,0.94)↓
Asian		0.67(0.63,0.71)↓
Other		1.05(1.01,1.09)↑
Dual Ever	Non-Dual Non-LIS	0.66(0.64,0.68)↓
Non-Dual Lis		0.66(0.63,0.70)↓
Living In Rural Area	No	0.94(0.92,0.95)↓
Medicare Part D Since 2008	Medicare Part D Since 2007	1.03(1.00,1.07)
Medicare Part D Since 2009		1.11(1.07,1.15)↑
Medicare Part D Since 2010		1.16(1.12,1.21)↑
Medicare Part D Since 2011		1.17(1.13,1.22)↑
Medicare Part D Since 2012		1.12(1.08,1.16)↑
Medicare Part D Since 2013		1.03(1.00,1.07)
Medicare Part D Since 2013		1.05(1.01,1.09)↑
Medicare Part D Since 2015		0.91(0.87,0.96)↓
Medicare Part D Since 2016		0.93(0.19,4.55)
AMI	No	0.74(0.69,0.79)↓
Atrial Fibrillation	No	0.94(0.91,0.97)↓
Cataract	No	1.23(1.21,1.25)↑
Chronic Kidney Disease	No	0.92(0.89,0.94)↓
COPD	No	0.83(0.81,0.86)↓
Heart Failure	No	0.79(0.77,0.82)↓
Diabetes	No	0.98(0.96,0.99)↓
Glaucoma	No	1.10(1.08,1.12)↑
Hip/Pelvic Fracture	No	0.68(0.60,0.77)↓
Ischemic Heart Disease	No	1.10(1.08,1.12)↑
Depression	No	1.17(1.13,1.21)
Alzheimer's Disease or Senile Dementia	No	0.67(0.63,0.71)↓
Osteoporosis	No	1.03(1.01,1.06)↑
Rheumatoid Arthritis/Osteoarthritis	No	2.84(2.80,2.89)↑
Stroke/Transient Ischemic Attack	No	0.97(0.94,1.01)
Breast Cancer	No	0.94(0.91,0.98)↓
Colorectal Cancer	No	0.79(0.74,0.85)↓

Prostate Cancer	No	1.03(0.99,1.07)
Lung Cancer	No	0.39(0.34,0.45)↡
Endometrial Cancer	No	0.85(0.77,0.94)↓
Anemia	No	1.01(0.99,1.03)
Asthma	No	1.27(1.24,1.31)↟
Hyperlipidemia	No	1.34(1.31,1.36)↟
Hyperplasia	No	1.13(1.10,1.16)↟
Hypertension	No	1.09(1.07,1.11)↟
Hypothyroidism	No	1.08(1.06,1.10)↟
Anxiety Disorders	No	0.98(0.96,1.01)
Bipolar Disorder	No	1.02(0.95,1.08)
Major Depressive Affective Disorder	No	1.06(1.02,1.10)↑
Schizophrenia and Other Psychotic Disorders	No	0.67(0.61,0.74)↡
Epilepsy	No	0.83(0.77,0.90)↡
Fibromyalgia, Chronic Pain and Fatigue	No	1.39(1.36,1.42)↟
Viral Hepatitis (General)	No	1.04(0.96,1.13)
Liver Disease Cirrhosis And Other Liver Conditions	No	0.95(0.92,0.99)↓
Leukemias and Lymphomas	No	0.94(0.88,1.01)
Migraine and Other Chronic Headache	No	1.28(1.23,1.33)↟
Mobility Impairments	No	0.70(0.65,0.76)↡
Obesity	No	1.04(1.02,1.06)↑
Peripheral Vascular Disease	No	1.00(0.97,1.04)
Tobacco Use Disorders	No	0.82(0.80,0.85)↡
Pressure Ulcers and Chronic Ulcers	No	0.82(0.77,0.87)↡
Deafness and Hearing Impairment	No	1.21(1.17,1.25)↟

Hazard ratios and confidence intervals from the primary analysis for Covariates except for the study antibiotics (which are in Table 3)

Abbreviations: HR, hazard ratio, CI, confidence interval; FLQ, fluoroquinolone; CIP, ciprofloxacin; LVX, levofloxacin; MXF, moxifloxacin; AMX, Amoxicillin; AMC, Amoxicillin Clavulanate; AZT, Azithromycin; LEX, Cephalexin.

↟= significantly high with P-value < 0.001, ↑= significantly high with 0.001 ≤ P-value < 0.05
↡= significantly low with P-value < 0.001, ↓= significantly high with 0.001 ≤ P-value < 0.05

Table 3. Hazard Ratios of Each Antibiotic by Anatomic Sites and Temporal Order of Drug Exposure

		Any Tendon Rupture	Achilles Tendon Rupture	Complete Rupture of Rotator Cuff	Other Tendon Ruptures	Death (Competing risk)
	Temporal Exposure	HR(95% CI)	HR(95% CI)	HR(95% CI)	HR(95% CI)	HR(95% CI)
AMX VS. NO AMX	≤ 30 days	0.86(0.80,0.92)↓	0.88(0.59,1.33)	0.88(0.82,0.95)↓	0.79(0.67,0.93)↓	0.66(0.61,0.71)↓
	31 – 60 days	0.94(0.87,1.01)	0.80(0.49,1.31)	0.91(0.84,0.99)↓	1.08(0.93,1.27)	0.69(0.63,0.75)↓
	≥ 61 days	1.00(0.98,1.02)	0.99(0.86,1.13)	1.01(0.99,1.04)	0.97(0.92,1.01)	0.77(0.75,0.78)↓
AMC VS. NO AMC	≤ 30 days	0.93(0.85,1.02)	1.25(0.79,1.97)	0.87(0.79,0.97)↓	1.17(0.98,1.41)	1.37(1.30,1.45)↑
	31 – 60 days	0.95(0.85,1.05)	1.37(0.82,2.29)	0.95(0.84,1.06)	0.81(0.63,1.04)	1.26(1.17,1.35)↑
	≥ 61 days	1.07(1.04,1.09)↑	0.95(0.81,1.12)	1.07(1.04,1.10)↑	1.02(0.96,1.08)	0.86(0.84,0.88)↓
AZM VS. NO AZM	≤ 30 days	0.99(0.93,1.06)	1.15(0.82,1.63)	1.00(0.93,1.08)	0.87(0.75,1.01)	0.80(0.75,0.84)↓
	31 – 60 days	0.90(0.84,0.98)↓	0.99(0.65,1.49)	0.91(0.84,0.99)↓	0.95(0.81,1.11)	0.77(0.73,0.82)↓
	≥ 61 days	1.07(1.05,1.09)↑	1.02(0.91,1.15)	1.09(1.07,1.12)↑	0.99(0.95,1.04)	0.71(0.70,0.72)↓
LEX VS. NO LEX	≤ 30 days	1.31(1.22,1.41)↑	1.93(1.35,2.75)↑	1.19(1.09,1.29)↑	1.79(1.56,2.06)↑	1.04(0.98,1.10)
	31 – 60 days	1.05(0.95,1.15)	1.14(0.66,1.96)	1.06(0.96,1.18)	1.02(0.82,1.26)	1.01(0.94,1.08)
	≥ 61 days	1.08(1.05,1.11)↑	1.00(0.85,1.16)	1.07(1.05,1.10)↑	1.15(1.09,1.21)↑	0.86(0.84,0.88)↓
LVX VS. NO LVX	≤ 30 days	1.14(1.05,1.25)↑	2.20(1.50,3.24)↑	1.16(1.06,1.28)↑	0.96(0.78,1.19)	2.19(2.11,2.28)↑
	31 – 60 days	1.09(0.98,1.21)	1.91(1.17,3.10)↑	1.09(0.97,1.22)	1.14(0.90,1.43)	1.80(1.71,1.89)↑
	≥ 61 days	1.02(1.00,1.05)	1.22(1.03,1.43)↑	1.03(1.00,1.07)↑	0.97(0.91,1.03)	0.99(0.97,1.01)
CIP VS. NO CIP	≤ 30 days	0.96(0.89,1.03)	1.06(0.70,1.60)	0.96(0.88,1.04)	0.84(0.71,1.00)↓	1.46(1.40,1.53)↑
	31 – 60 days	0.92(0.85,1.01)	1.02(0.63,1.67)	0.91(0.82,1.00)↓	0.95(0.78,1.14)	1.31(1.24,1.38)↑
	≥ 61 days	0.96(0.94,0.98)↓	1.16(1.02,1.32)↑	0.96(0.94,0.99)↓	0.92(0.88,0.97)↓	0.86(0.84,0.88)↓
MXF VS. NO MXF	≤ 30 days	0.59(0.37,0.93)	0.97(0.15,6.24)	0.52(0.30,0.91)↓	0.76(0.33,1.77)	2.05(1.78,2.35)↑
	31 – 60 days	0.71(0.43,1.15)	0.00(0.00,0.00)	0.63(0.35,1.13)	0.93(0.39,2.25)	1.43(1.18,1.72)↑
	≥ 61 days	0.99(0.93,1.06)	1.02(0.69,1.51)	0.99(0.92,1.06)	1.10(0.95,1.27)	0.89(0.86,0.93)↓
FLQ VS. AMX	≤ 30 days	1.00(0.84,1.19)	1.49(0.69,3.19)	0.94(0.77,1.16)	1.08(0.77,1.50)	2.86(2.61,3.13)↑
	31 – 60 days	0.95(0.79,1.15)	0.07(0.04,0.12)↓	0.94(0.75,1.17)	0.92(0.65,1.31)	2.18(1.96,2.44)↑
	≥ 61 days	0.99(0.96,1.02)	1.14(0.94,1.40)	0.98(0.95,1.02)	1.03(0.96,1.11)	1.19(1.16,1.22)↑
FLQ VS. AZM	≤ 30 days	0.87(0.73,1.03)	1.14(0.54,2.39)	0.83(0.68,1.02)	0.98(0.70,1.37)	2.35(2.18,2.53)↑
	31 – 60 days	0.99(0.82,1.19)	0.06(0.04,0.09)↓	0.93(0.75,1.16)	1.06(0.75,1.49)	1.94(1.77,2.13)↑
	≥ 61 days	0.93(0.90,0.96)↓	1.10(0.91,1.34)	0.91(0.88,0.94)↓	1.00(0.93,1.08)	1.29(1.25,1.32)↑
FLQ VS. LEX	≤ 30 days	0.66(0.55,0.78)↓	0.68(0.32,1.42)	0.70(0.57,0.87)↓	0.47(0.34,0.66)↓	1.80(1.67,1.95)↑
	31 – 60 days	0.85(0.70,1.04)	0.05(0.03,0.09)↓	0.80(0.64,1.01)	0.99(0.68,1.44)	1.48(1.34,1.64)↑
	≥ 61 days	0.92(0.89,0.95)↓	1.13(0.92,1.40)	0.92(0.89,0.96)↓	0.86(0.80,0.93)↓	1.06(1.03,1.09)↑
FLQ VS. AMC	≤ 30 days	0.93(0.77,1.11)	1.05(0.48,2.32)	0.96(0.77,1.19)	0.72(0.51,1.02)	1.37(1.27,1.48)↑

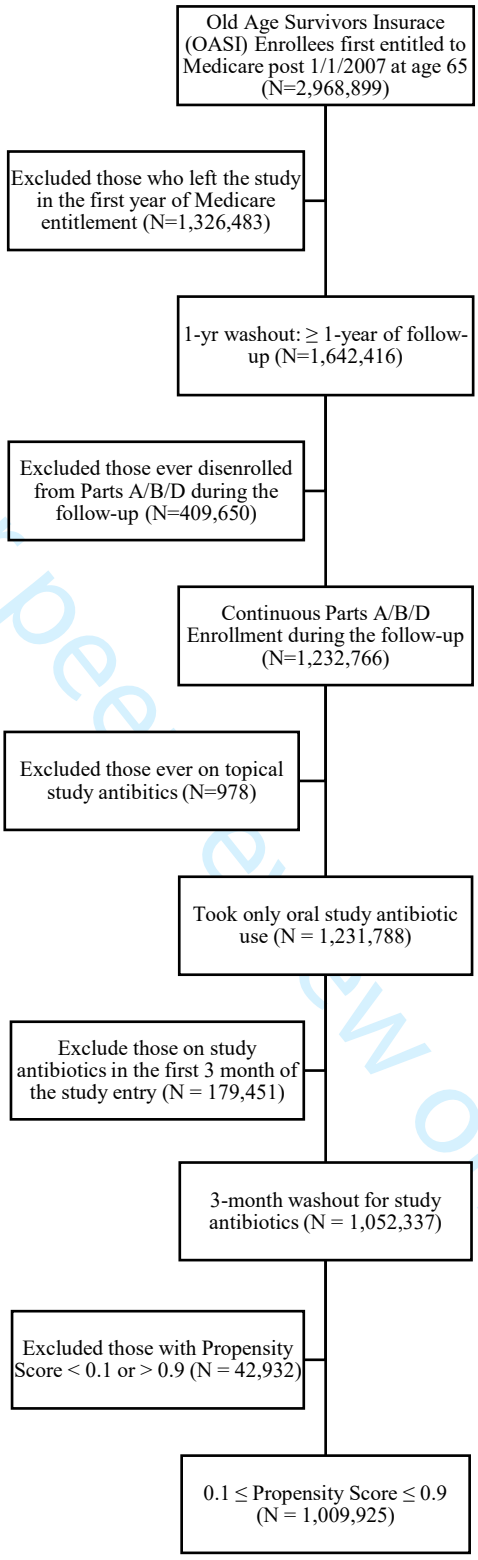
	31 – 60 days	0.94(0.77,1.15)	0.04(0.02,0.07) ↓	0.90(0.72,1.14)	1.24(0.83,1.86)	1.19(1.08,1.31) ↑
	≥ 61 days	0.93(0.90,0.97) ↓	1.19(0.95,1.49)	0.93(0.89,0.96) ↓	0.98(0.90,1.06)	1.06(1.03,1.09) ↑

Abbreviations: HR, hazard ratio, CI, confidence interval; FLQ, fluoroquinolone; CIP, ciprofloxacin; LVX, levofloxacin; MXF, moxifloxacin; AMX, Amoxicillin; AMC, Amoxicillin Clavulanate; AZT, Azithromycin; LEX, Cephalexin.
↑= significantly high with P-value < 0.001, ↑= significantly high with 0.001 ≤ P-value < 0.05
↓= significantly low with P-value < 0.001, ↓= significantly high with 0.001 ≤ P-value < 0.05

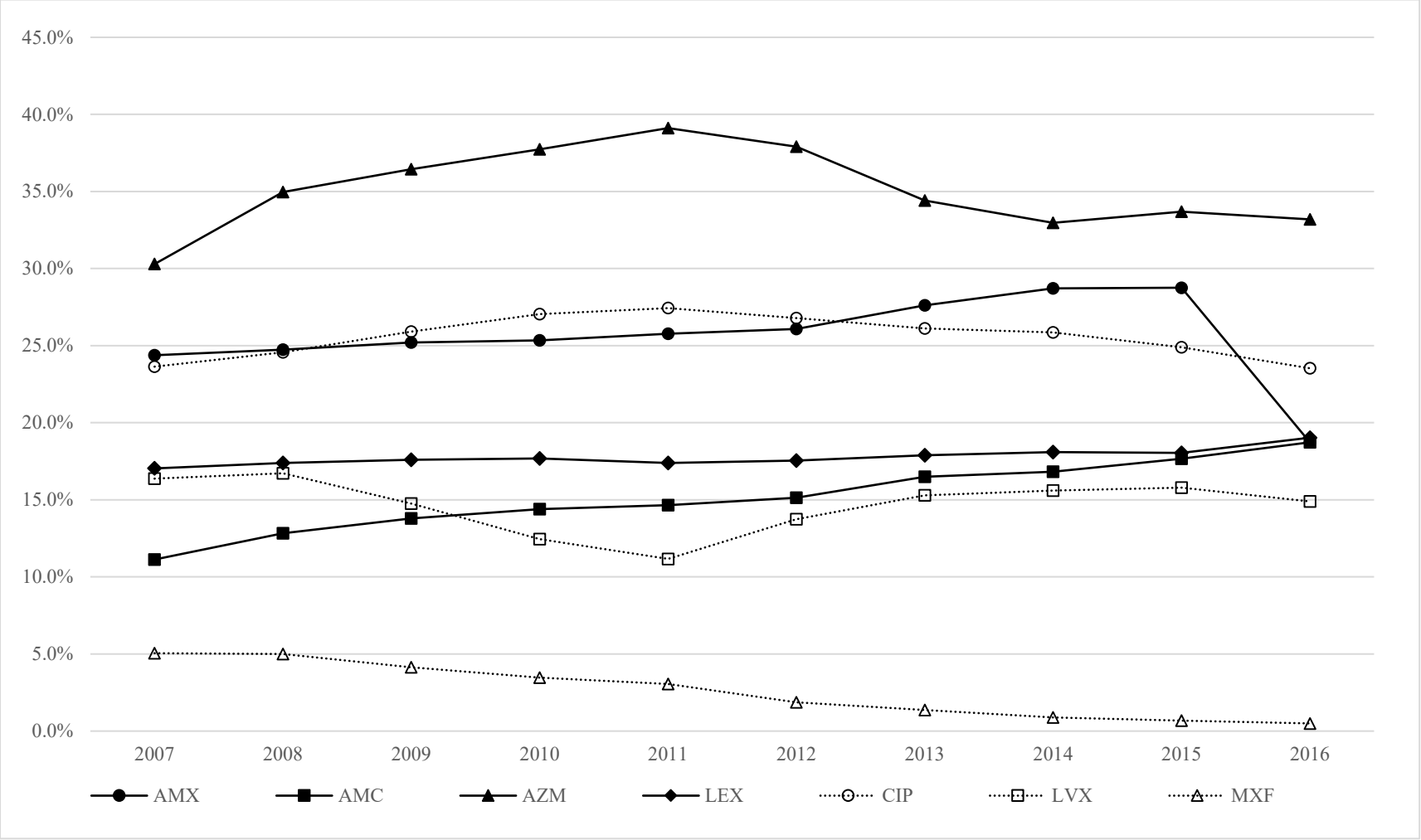
Table 4. Pairwise Comparisons

Comparison	Temporal Exposure	Any Tendon Rupture HR(95% CI)	Achilles Tendon Rupture HR(95% CI)	Complete Rupture of Rotator Cuff HR(95% CI)	Other Tendon Rupture HR(95% CI)	Death (Competing risk) HR(95% CI)
HRs comparing use of each FQ with use of each non-FQ antibiotics in a ≤30-day window						
CIP VS. LVX	**≤ 30 days**	0.84(0.75,0.94)↓	0.48(0.27,0.86) ↓	0.82(0.73,0.94) ↓	0.87(0.67,1.15)	0.67(0.63,0.71)↓↓
CIP VS. MXF	**≤ 30 days**	1.63(1.02,2.61)↑	1.08(0.16,7.29)	1.84(1.05,3.24)↑	1.10(0.47,2.60)	0.72(0.62,0.83)↓↓
LVX VS. MXF	**≤ 30 days**	1.95(1.21,3.13)↑	2.26(0.34,15.17)	2.24(1.27,3.94)↑	1.26(0.53,3.01)	1.07(0.93,1.24)
CIP VS. AMX	**≤ 30 days**	1.11(1.01,1.23)↑	1.20(0.66,2.16)	1.09(0.97,1.21)	1.06(0.84,1.34)	2.23(2.05,2.44)↑↑
CIP VS. AZM	**≤ 30 days**	0.97(0.87,1.06)	0.91(0.53,1.57)	0.96(0.86,1.07)	0.96(0.77,1.21)	1.84(1.71,1.97)↑↑
CIP VS. LEX	**≤ 30 days**	0.73(0.66,0.81)↓↓	0.55(0.31,0.95) ↓	0.81(0.72,0.91)↓↓	0.47(0.37,0.59)↑↑	1.41(1.31,1.52)↑↑
CIP VS. AMC	**≤ 30 days**	1.03(0.91,1.16)	0.84(0.46,1.56)	1.10(0.96,1.25)	0.71(0.56,0.92)↓	1.07(1.00,1.15)
LVX VS. AMX	**≤ 30 days**	1.33(1.19,1.49)↑↑	2.50(1.45,4.29)↑	1.32(1.16,1.49)↑↑	1.22(0.93,1.59)	3.34(3.07,3.64)↑↑
LVX VS. AZM	**≤ 30 days**	1.15(1.03,1.29)↑	1.91(1.13,3.23)↑	1.16(1.03,1.31)↑	1.10(0.84,1.44)	2.75(2.57,2.95)↑↑
LVX VS. LEX	**≤ 30 days**	0.87(0.78,0.98) ↓	1.14(0.68,1.92)	0.98(0.86,1.12)	0.54(0.41,0.69)↑↑	2.11(1.97,2.27)↑↑
LVX VS. AMC	**≤ 30 days**	1.23(1.08,1.40)↑	1.76(0.98,3.15)	1.33(1.15,1.54)↑↑	0.82(0.62,1.08)	1.60(1.49,1.72)↑↑
MXF VS. AMX	**≤ 30 days**	0.68(0.43,1.09)	1.10(0.16,7.41)	0.59(0.34,1.03)	0.96(0.41,2.27)	3.12(2.67,3.65)↑↑
MXF VS. AZM	**≤ 30 days**	0.59(0.37,0.94) ↓	0.84(0.13,5.65)	0.52(0.30,0.91)↓	0.88(0.37,2.07)	2.57(2.21,2.98)↑↑
MXF VS. LEX	**≤ 30 days**	0.45(0.28,0.72) ↓	0.50(0.08,3.35)	0.44(0.25,0.77)↓	0.43(0.18,1.00)	1.97(1.70,2.‡29)↑↑
MXF VS. AMC	**≤ 30 days**	0.63(0.39,1.01)	0.78(0.11,5.33)	0.60(0.34,1.05)	0.65(0.28,1.53)	1.50(1.29,1.73)↑↑
HRs comparing use of FQ as a class with use of each non-FQ antibiotics across different time window						
FLQ VS. AMX	**Overall**	0.98(0.90,1.07)	0.49(0.36,0.68)	0.95(0.86,1.06)	1.01(0.86,1.19)	1.95(1.86,2.05)↑↑
FLQ VS. AZM	**Overall**	0.93(0.85,1.01)	0.42(0.30,0.57)	0.89(0.80,0.98)↓	1.01(0.86,1.19)	1.80(1.73,1.88)↑↑
FLQ VS. LEX	**Overall**	0.80(0.73,0.88)	0.34(0.24,0.47)	0.80(0.72,0.89)	0.74(0.62,0.88)	1.42(1.35,1.48)↑↑
FLQ VS. AMC	**Overall**	0.93(0.85,1.02)	0.37(0.26,0.52)	0.93(0.83,1.03)	0.96(0.80,1.15)	1.20(1.15,1.25)↑↑

Abbreviations: HR, hazard ratio, CI, confidence interval; FLQ, fluoroquinolone; CIP, ciprofloxacin; LVX, levofloxacin; MXF, moxifloxacin; AMX, Amoxicillin; AMC, Amoxicillin Clavulanate; AZT, Azithromycin; LEX, Cephalexin.
↑↑= significantly high with P-value < 0.001, ↑= significantly high with 0.001 ≤ P-value < 0.05
↓↓= significantly low with P-value < 0.001, ↓= significantly high with 0.001 ≤ P-value < 0.05



Supplementary Figure. Secular Trend of Study Antibiotic Use



X-axis: Calendar year.

Y-axis: % of patients on each drug class.

STROBE Statement—Checklist of items that should be included in reports of ***case-control studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	6
		(*b*) For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	8-9
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-9
		(*b*) Describe any methods used to examine subgroups and interactions	n/a
		(*c*) Explain how missing data were addressed	n/a
		(*d*) If applicable, explain how matching of cases and controls was addressed	n/a
		(*e*) Describe any sensitivity analyses	n/a
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	9
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9-10
		(b) Indicate number of participants with missing data for each variable of interest	n/a
Outcome data	15*	Report numbers in each exposure category, or summary measures of exposure	10

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-14
		(*b*) Report category boundaries when continuous variables were categorized	12-13
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14-17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

*Give information separately for cases and controls.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.