USING REAL WORLD DATA TO EXAMINE THE ASSOCIATION BETWEEN FLUOROQUINOLONE USE AND AORTIC ANEURYSM AND DISSECTION

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OBJECTIVES

In December 2018, the FDA decided the increased risk of aortic aneurysm (AA) and dissection (DN) due to fluoroquinolone (FQ) use warranted the inclusion of a warning on prescribing information. Our objectives were to:

1. Measure the increased risk of AA and DN related to FQ use in a real world data set (primary analysis).
2. Conduct sensitivity analyses to assess assumptions made in the primary analysis.
3. Perform a quantitative bias analysis (QBA)[1] to correct for non-differential misclassification of exposure (NDME).

METHODS

The primary analysis compared ① FQ to ④ AC utilizing the TNX platform and reproducing a publication cited by the FDA.[2] The index event (IE) was the first FQ/AC recorded post-2008. A matched (1:1) propensity score analysis examined the occurrence of AA and DN in the 60 days after the IE, producing adjusted risk ratios (RRs) and 95% confidence intervals (CIs).

Sensitivity analyses compared:

1. ⑤ FQ to ⑥ AC after restricting the sample
2. The classes of drugs: ① FQ to ② penicillin (PC).
3. The specific drug ingredients: ③ ciprofloxacin (CP) to ④ AC.
4. ① FQ to ④ AC with a 30-day follow up period.

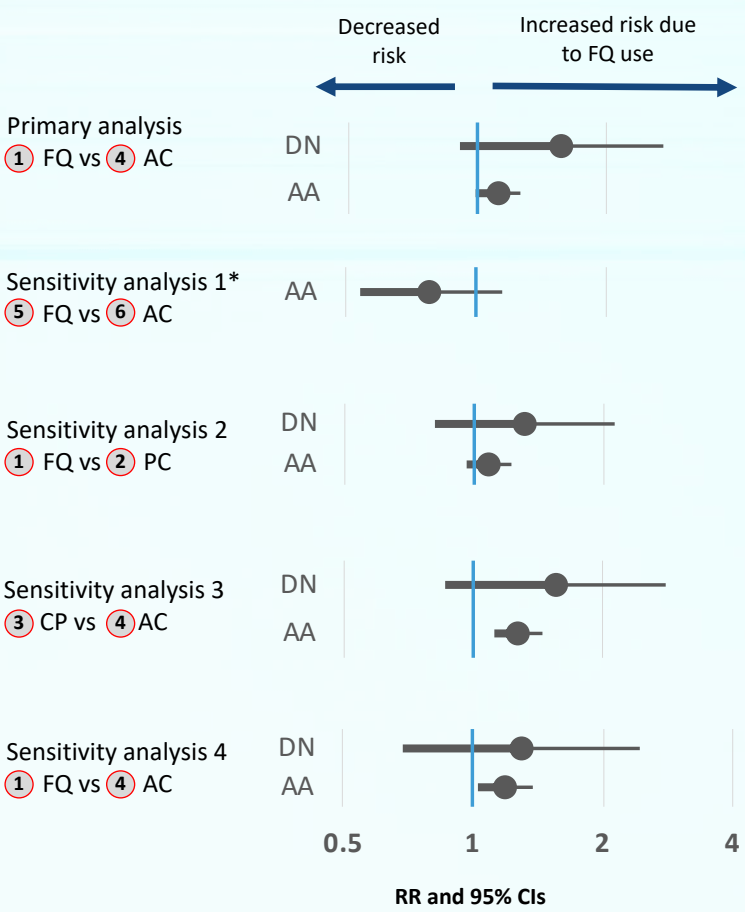
A QBA corrected for NDME in the primary analysis, under two different scenarios:

1. Imperfect identification of FQ use, with a relatively low sensitivity.
2. Imperfect identification of FQ use, with a relatively high sensitivity.

In both scenarios, specificity was reduced. A min, max and mode value defined distributions of sensitivity and specificity (bias parameters). In each scenario, sensitivity and specificity values were randomly selected from the distributions (Figure 2), these values were then applied to the contingency table results of the primary analysis, and a revised RR was calculated. The 2.5th and 97.5th percentile defined the bounds of a 95% credible interval after 10,000 iterations (Table 2).

RESULTS OF SENSITIVITY ANALYSES

In the primary analysis, 134,662 patients in each cohort were matched by propensity score (Table 1). In all but one instance, the sensitivity analyses did not meaningfully change the interpretation of the results. When restricting to a smaller sample of patients, the AA effect estimate shifted from above to below the null value of one (not significant).



*Results related to the occurrence of DN not shown due to small sample size.

1. Lash TL, Fox MP, Fink AK. Applying Quantitative Bias Analysis to Epidemiologic Data. Springer Science & Business Media; 2011. Pasternak B, Inghammar M, Svanström H. 2. Fluoroquinolone use and risk of aortic aneurysm and dissection: nationwide cohort study. BMJ. 2018;360:678.

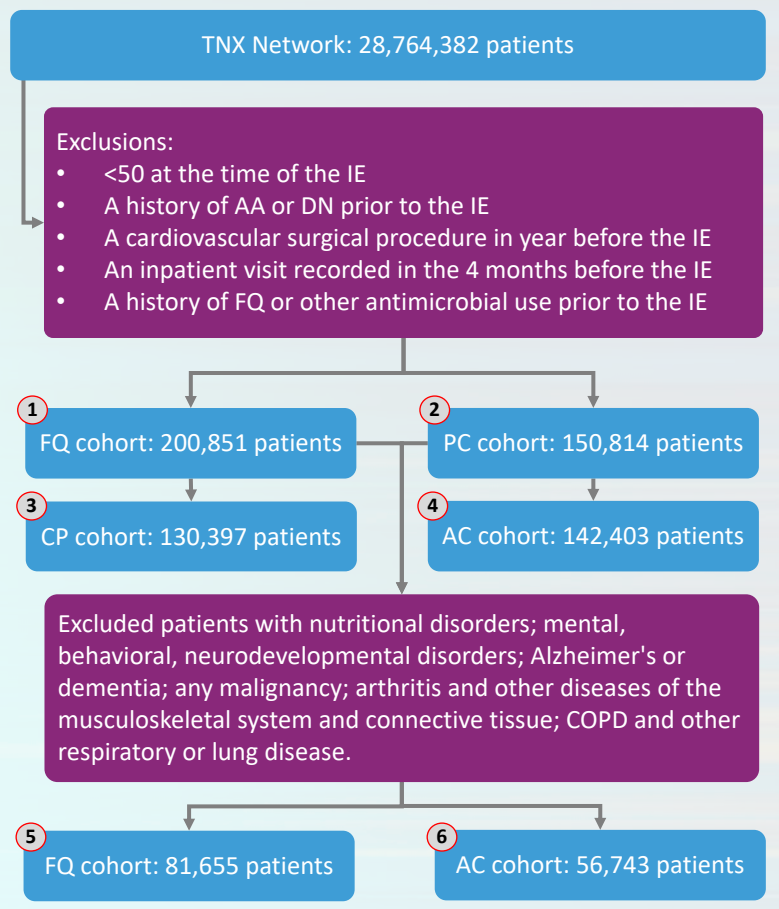


Figure 1. Patient flow diagram (counts before matching)

	Before Matching		After Matching	
	FQ	AC	FQ	AC
Age at index (Mean +/- SD)	68.7 +/- 9.6	65.8 +/- 9.1	66.3 +/- 9.0	66.2 +/- 9.1
Female (%)	54.5	56.7	57.3	56.4
White (%)	76.1	79.6	79.4	79.0
Outcome: AA	--	--	527	472
Outcome: DN	--	--	33	21

Note: standardized mean difference <10% for all comparisons after matching

Table 1. Characteristics before/after matching in primary analysis

RESULTS OF QBA

In both QBA scenarios, correcting for NDME increased the RR (Table 2). When FQ use was assumed to be misclassified to a greater degree than the comparison medication (lower sensitivity scenario), the magnitude of the increase in the RR was more substantial (1.53 and 5.06 for AA and DN).

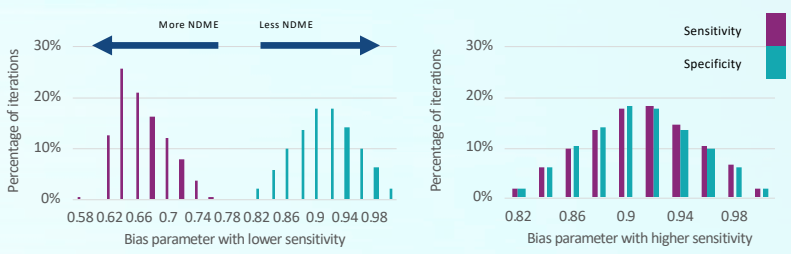


Figure 2. Distribution of bias parameters

		AA		DN	
		RR	Credible interval	RR	Credible interval
Primary analysis results		1.12	(0.99, 1.26)	1.57	(0.91, 2.72)
QBA results	Lower sensitivity	1.53	(1.16, 11.48)	5.06	(1.92, 84.11)
	Higher sensitivity	1.15	(1.02, 1.30)	1.78	(1.02, 3.07)

Table 2. Results of QBA

CONCLUSIONS

Although all results were not statistically significant, the direction of the effect estimate comparing FQ to other treatments supported the FDA-cited findings. FQ use is likely to be misclassified if patients switch to other antibiotics after the initial prescription, potentially due to increased awareness of the risk of AA, DN, and other side effects. This misclassification likely attenuates the association between FQ use and AA/DN. To our knowledge, this is the first use of QBA to examine FQ use.