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Effects of fluoroquinolone on mitral and aortic regurgitation: A systematic review and meta-analysis

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ABSTRACT

This study aimed to systematically review and meta-analyze the effects of fluoroquinolones on mitral and aortic regurgitation. Seven electronic databases were searched for relevant research data published in English and Thai between the database's inception and September 30, 2022, including additional records from Silpakorn University and Chulalongkorn University's online theses databases. This systematic review included studies that compared the effects of fluoroquinolones and other antibiotic classes on the occurrence of mitral and aortic valve regurgitation. Subsequently, the quality of the research was evaluated using the Newcastle-Ottawa Quality Assessment Scale. Of the 2,891 articles identified, two eligible studies were included in the analysis. The meta-analysis examined different exposure periods and discovered that individuals who received fluoroquinolones within 30 days and within one year had a similar risk of developing mitral and aortic valve regurgitation compared to those who received other groups of antibiotics. Specifically, the risk of mitral and aortic regurgitation associated with fluoroquinolones was comparable to that of amoxicillin and macrolides. Overall, the meta-analysis found no association between fluoroquinolone use and the development of mitral and aortic regurgitation.

Keywords: fluoroquinolones; mitral regurgitation; aortic regurgitation; valvular heart disease; systematic review

1. INTRODUCTION

Fluoroquinolones are among the most often prescribed antibiotics due to their broad spectrum of action and strong propensity to diffuse throughout tissues (Etminan et al., 2012). The broad antibacterial property of fluoroquinolones is due to an ability to inhibit DNA synthesis through the inhibition of both DNA gyrase and topoisomerase IV, which are essential for cellular replication and bacterial growth (Carino et al., 2019). Medicines of this class are currently used to treat a variety of disorders. Fluoroquinolone prescription accounts for 24% of all antibiotic prescriptions in the United States (Kabbani et al., 2018). Noticeably, fluoroquinolone is the third most widely prescribed group of antibiotics in the treatment of adult outpatients, prescribed to 30 million outpatients in the United States each year (Pasternak et al., 2018). In addition, a study from India showed that

fluoroquinolones are the most widely prescribed antibiotic class in pharmacies, private clinics and hospitals. Fluoroquinolones were mostly prescribed in urban hospitals, accounting for 43.6% of all antibiotic prescriptions (Chandy et al., 2013). By focusing on antibiotic use in Thailand, fluoroquinolones account for 11% (around 13 million defined daily doses) of all antibiotic prescriptions of outpatients under the universal coverage scheme (UCS), and the use of fluoroquinolones has statistically significantly increased (La-ongsuwan et al., 2017; Thammatacharee et al., 2017).

Multiple types of adverse effects of fluoroquinolones have been reported, including side effects that affect tendons, joints, nerves, and mitral and aortic valve regurgitation, which are related to collagen degradation. This can lead to long-term impairment, permanent disability, or even death in some patients (Etminan et al., 2012; Hull University Teaching Hospitals, 2019). Additionally, earlier research conducted in the United States revealed that taking fluoroquinolones was associated with an increased risk of mitral and aortic regurgitation, which can lead to death in some patients. The biological plausibility is that fluoroquinolones can damage collagen and other structural components of the extracellular matrix, which are essential structural components of the mitral and aortic valves. Nevertheless, research conducted outside the United States indicated that receiving fluoroquinolones was not associated with mitral and aortic regurgitation compared to individuals receiving penicillin V, macrolides, and amoxicillin groups (Etminan et al., 2019; Pasternak et al., 2018; Strange et al., 2021; Tanne, 2008).

There is no obvious conclusion from the preliminary literature review on the impact of fluoroquinolones on mitral and aortic regurgitation. As a result, investigations on the effects of these medications on heart valves are not yet available. A systematic literature review and meta-analysis of mitral and aortic regurgitation will assist in gathering information. Medical staff, practitioners, and administrators can benefit from empirical data in deciding how fluoroquinolones should be used. Additionally, potential adverse effects will be monitored, and procedures to prevent adverse effects from using this class of drugs will be established.

2. MATERIALS AND METHODS

2.1 Search strategy

A systematic literature search was performed in four foreign electronic databases, including PubMed Central (PMC), ScienceDirect, Scopus, and Cochrane, as well as three Thai research databases, which included: Thai-Journal Citation Index (TCI), ThaiLis, and Health Intervention and Technology Assessment Program (HITAP), along with additional searches from theses and dissertation online databases from Silpakorn University and Chulalongkorn University.

All databases were searched using related keywords such as “fluoroquinolones,” “aortic regurgitation,” “mitral regurgitation,” “aortic valve insufficiency,” “mitral valve insufficiency,” “*oxacin,” and “heart and safety” and using Medical Subject Headings (MeSH) terms for PubMed database. In addition, “AND” and “OR” are Boolean Operators used to refine the search.

2.2 Eligible criteria

After the initial search, inclusion and exclusion criteria were developed based on the PICOS framework (Centre for Reviews and Dissemination, 2009), which considered participant (P), intervention (I), comparison (C), outcome (O), and study design (S). To be included, each study had to meet all the following criteria. Participant: individuals who received antibiotics. Intervention: administration of fluoroquinolones. Comparison: use of fluoroquinolones versus other antibiotic classes. Outcome: the occurrence of organic mitral regurgitation and organic aortic regurgitation. Study design: we included grey literature, randomized controlled trials (RCTs), cohort, case-control, or cross-sectional study. Additionally, studies published in either English or Thai between the inception of each database and September 30, 2022, were included in this systematic appraisal.

Studies that compared different drugs within the fluoroquinolones class were excluded. Addition exclusion criteria were studies without unavailable full-text and those not published in English or Thai.

2.3 Data extraction

Titles, abstracts, and full articles were screened based on the selection criteria. To reduce bias, two reviewers separately extracted the study characteristics and results of the included studies, which share the same perspectives on the results. For each included study, the following data were extracted and tabulated: authors, year of publication, location of study, study design, period of investigation, number of participants, age, number of males included, drug regimen used, points-of-time for assessment, and outcomes.

2.4 Quality assessment

To determine the quality of the included studies, two reviewers independently scored included studies based on the Newcastle-Ottawa Quality Assessment Scale (NOS) (Wells et al., 2000), which shared the same perspective on the results. All included studies needed to achieve a minimum score of 4 on the NOS. The quality assessment forms selected differed depending on the research design of the selected study.

2.5 Statistical analysis

All statistical analyses were carried out using STATA version 17.0 software. The Cochrane chi-squared (Q-test) tool (p-value threshold set at 0.10) and the I^2 tool were used to evaluate the heterogeneity of studies, where the I^2 value >30% indicated heterogeneity between studies. Data were pooled using random effects after tests of heterogeneity. To analyze the outcomes with binary data, the combined results were given as an odds ratio (OR) value along with a 95% CI. These findings were presented graphically using a forest plot. In addition, publication bias was assessed by visual inspection of the funnel plot (Ket-Aim et al., 2005; Saokaew, 2016; van Enst et al., 2014).

3. RESULTS AND DISCUSSION

3.1 Study selection

A total of 2,891 articles were identified in the initial search. After removing 185 duplicate records, 2,706 articles remained for full-text screening. After an extensive review

and application of inclusion and exclusion criteria, 2,704 articles were excluded due to publication in languages other than English or Thai (n = 21), comparison between drugs within the fluoroquinolones class (n = 56), research not related to mitral and aortic regurgitation (n = 2,235), studies that did not compared fluoroquinolones with other antibiotic classes (n = 388), and studies not focused on organic valve regurgitation (n = 4). Ultimately, two studies met all the criteria and were included in this review (Figure 1).

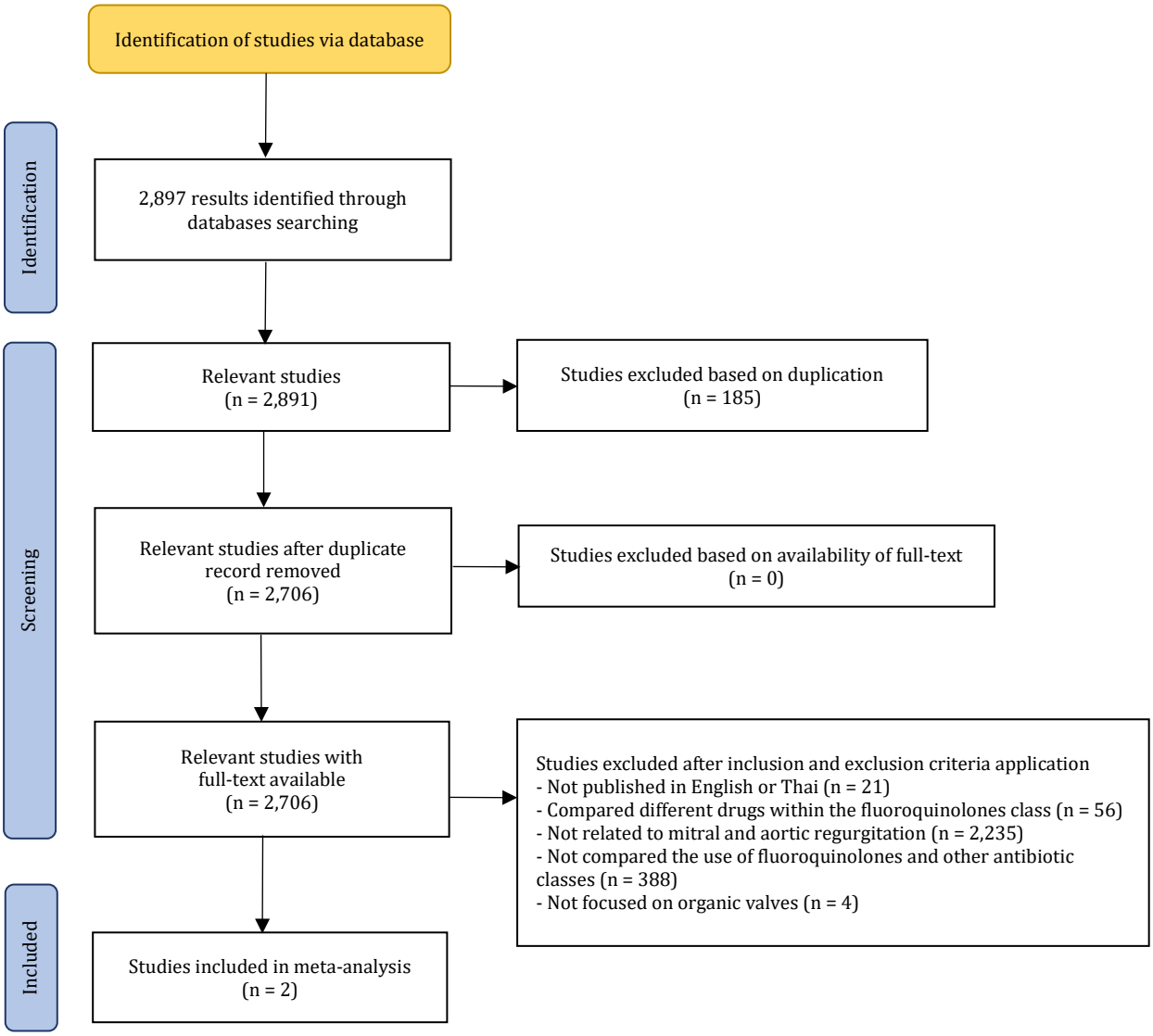

Figure 1. PRISMA 2020 flow diagram (PRISMA, 2021) of the included studies

3.2 Study characteristics

The two included studies both utilized a nested case-control study design and were conducted in the United States and Denmark. Both studies were published in English in 2019 and 2021, respectively. Each study examined the association between fluoroquinolone exposure and the incidence of mitral and aortic valve regurgitation and compared with other antibiotics classes. In the fluoroquinolones groups, participants received ciprofloxacin, levofloxacin, moxifloxacin, or gemifloxacin, while the comparison groups received amoxicillin, macrolides, and penicillin V. One study reported an association between fluoroquinolones exposure and mitral and aortic regurgitation, whereas the other did not observe such an association (Table 1).

Additionally, Both studies also reported participants' comorbidities, which included myocardial infarction, ischemic heart disease, heart failure, atrial fibrillation, ischemic stroke/transient ischemic attack (TIA), coronary artery disease, hypertension, diabetes mellitus, chronic obstructive pulmonary disease (COPD), and chronic kidney disease. Furthermore, concomitant pharmacotherapies included beta-blockers, calcium channel blockers, RAS inhibitors, loop diuretics, non-loop diuretics, statins, cabergoline, pergolide, phentermine, acetylsalicylic acid, ADP inhibitor, and oral coagulants.

Table 1. Extracted data from each included study

Author, Year	Study location	Study design	Period of investigation	Number of participants		Age (years)		Number of male/female		Drug regimens used		Points-of-time for assessment	Outcomes
				FQ group	Non-FQ group	FQ group	Non-FQ group	FQ group	Non-FQ group	FQ group	Non-FQ group		
Etminan et al., 2019	USA	Nested case-control Database: U.S. PharMetrics Plus (IQIA)	2006–2016	12,502	125,020	58.1 ± 12.7	58.1 ± 12.7	7,307/5,195	70,370/54,650	Ciprofloxacin, Levofloxacin, Moxifloxacin, Gemifloxacin	Amoxicillin	Within 30 days	Adjusted RRs = 2.40 (95% CI 1.82, 3.16)
												Within days 31–60	Adjusted RRs = 1.47 (95% CI 1.03, 2.09)
												Within days 61–365	Adjusted RRs = 1.06 (95% CI 0.91, 1.21)
											Azithromycin	Within 30 days	Adjusted RRs = 1.75 (95% CI 1.34, 2.29)
												Within days 31–60	Adjusted RRs = 1.37 (95% CI 0.95, 1.98)
												Within days 61–365	Adjusted RRs = 1.18 (95% CI 1.01, 1.38)

Table 1. Extracted data from each included study (continued)

Author, Year	Study location	Study design	Period of investigation	Number of participants		Age (years)		Number of male/ female		Drug regimens used		Points-of-time for assessment	Outcomes
				FQ group	Non-FQ group	FQ group	Non-FQ group	FQ group	Non-FQ group	FQ group	Non-FQ group		
Strange et al., 2021	Denmark	Nested case-control Database: The Danish National Patient Register (DNPR)	2005–2018	<u>Based on diagnostic code:</u>									
				38,370	1,151,100	58.1 ± 12.7	Median age = 70 (IQR 61–78)	Median age = 70 (IQR 61–78)	567,720/ 582,380	Ciprofloxacin, Moxifloxacin	Penicillin V	Within 30 days	HR = 0.91 (95% CI 0.67, 1.24)
												Within 90 days	HR = 0.92 (95% CI 0.81, 1.06)
												Within 1 year	HR = 1.02 (95% CI 0.95, 1.09)
				<u>Based on surgical interventions:</u>									
				4,008	120,240	Median age = 66 (IQR 57–73)	Median age = 66 (IQR 57–73)	2,736/ 1,272	82,080/ 38,160	Ciprofloxacin, Moxifloxacin	Penicillin V	Within 1 year	HR = 0.81 (95% CI 0.65, 1.02)
												Within 3 years	HR = 0.96 (95% CI 0.84, 1.11)
				<u>From supplementary material:</u>									
				38,370	1,151,100	Median age = 70 (IQR 61–78)	Median age = 70 (IQR 61–78)	18,924/ 19,446	567,720/ 583,380	Ciprofloxacin, Moxifloxacin	Amoxicillin	Within 90 days	HR = 0.73 (95% CI 0.57, 0.79)
												Within 1 year	HR = 0.71 (95% CI 0.64, 0.79)
											Macrolides	Within 90 days	HR = 0.77 (95% CI 0.63, 0.95)
												Within 1 year	HR = 0.82 (95% CI 0.75, 0.89)

3.3 Quality assessment

Two independent evaluators assessed the quality of the selected studies, and both reached consensus on their judgments; therefore, consultation with a third evaluator was not required. To determine the quality of the included studies, the NOS for case-control studies, was used to evaluate. The two included nested case-control studies achieved scores of 4 and 5, respectively.

3.4 Meta-analysis results

3.4.1 Effects of fluoroquinolones on mitral and aortic regurgitation at different time points

Meta-analysis of the included studies showed that fluoroquinolones was not associated with an increased risk of mitral and aortic regurgitation among patients who received the drugs within 30 days (OR = 1.34, 95% CI 0.59, 3.07; I^2 = 98.02%). Similarly, there was no significant association noted in patients who received fluoroquinolones within one year (OR = 1.15, 95% CI 0.71, 1.87; I^2 = 98.96%) (Figure 2).

3.4.2 Effects of fluoroquinolones on mitral and aortic regurgitation compared to other antibiotics classes

Considering the effect of fluoroquinolones on mitral and aortic regurgitation in patients receiving fluoroquinolones and those receiving other classes of antibiotics, the analysis found no significant difference, Specifically, patients who received fluoroquinolones had a similar risk of developing a mitral or aortic regurgitation as those receiving amoxicillin (OR = 0.97, 95% CI 0.44, 2.14; I^2 = 99.44%) or macrolides (OR = 1.10, 95% CI 0.60, 2.00; I^2 = 99.03%) (Figure 3).

The heterogeneity analysis showed that the p-value of the chi-squared statistic test was less than 0.10, and the I^2 statistic ranged from 98.02% to 99.04%, indicating high heterogeneity among the included studies. Therefore, a random-effects model was employed for the meta-analysis based on the heterogeneity of the included studies. By focusing on the publication bias, and visual inspection of funnel plots, no publication bias was indicated.

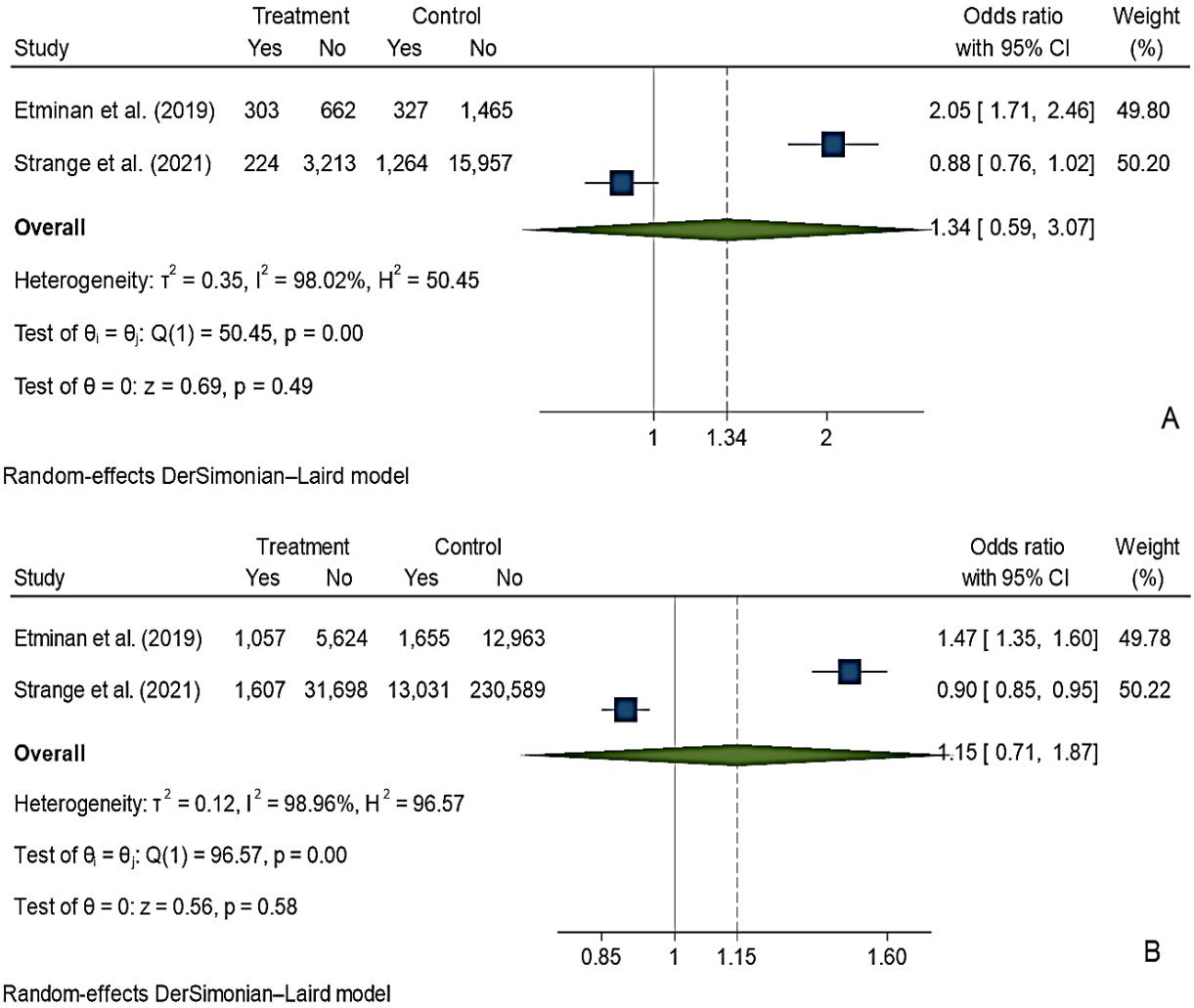

Figure 2. Forest plot from the meta-analysis illustrating the association between fluoroquinolone use and the risk of mitral and aortic regurgitation at different time points: (A) individuals who received fluoroquinolones within 30 days, (B) individuals who received fluoroquinolones within one year

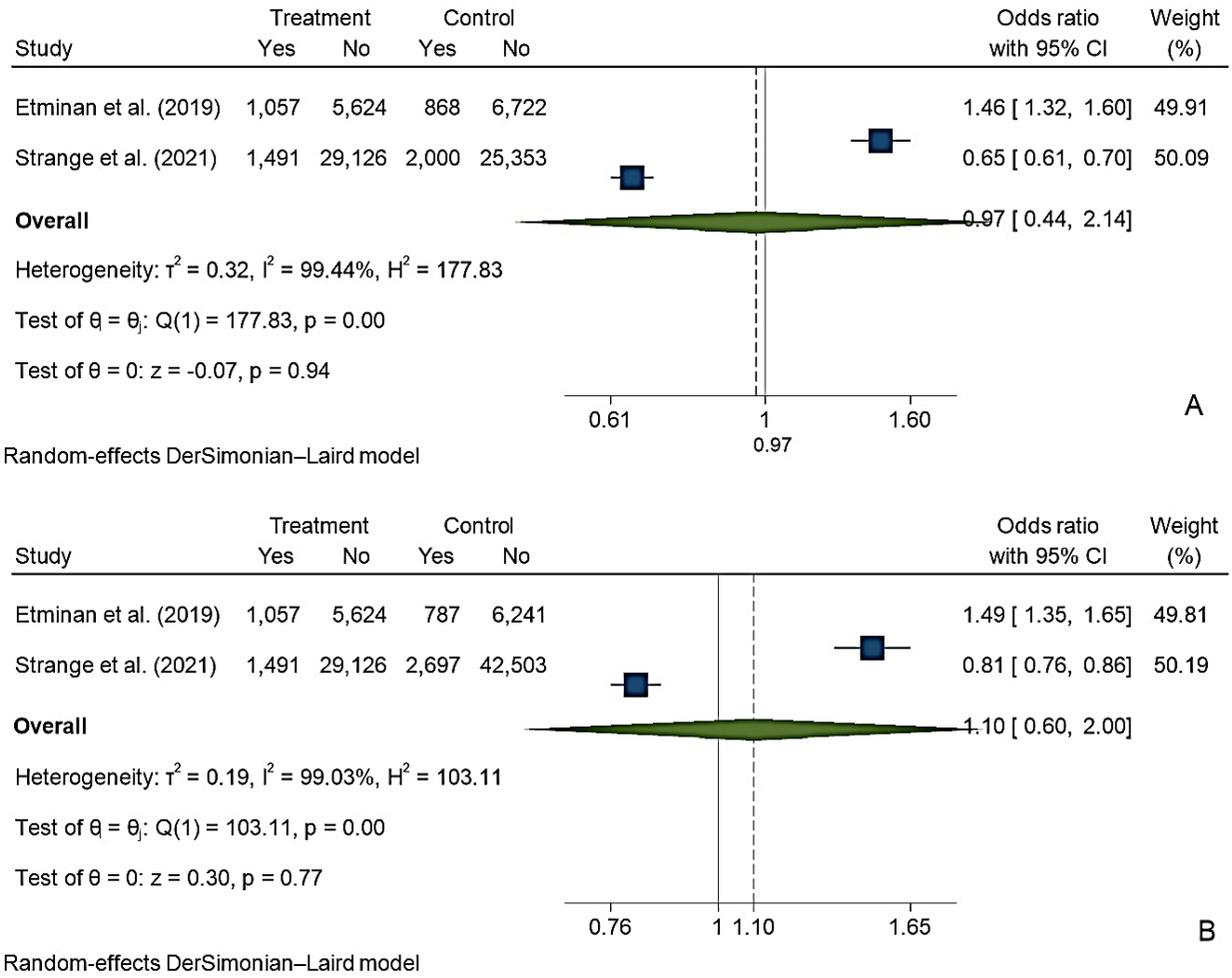

Figure 3. Forest plot from the meta-analysis showing the association between fluoroquinolone use and the risk of mitral and aortic regurgitation compared to other classes of antibiotics: (A) comparison with individuals who received amoxicillin, and (B) comparison with individuals who received macrolides

3.5 Discussion

The findings of this meta-analysis indicate that fluoroquinolones are not associated with an increased risk of mitral and aortic regurgitation compared to other antibiotic classes. This result contrasts with the findings from a case report by Schjøtt and Messner (2018), which demonstrated an association between fluoroquinolone use and increased risk of mitral and aortic regurgitation. (Schjøtt & Messner, 2018).

The reason for the different findings may be the distinction in research methods, information sources, type of fluoroquinolones and comparator antibiotics included, and the assessment time points for assessment. Strange et al. (2021) gathered data from a Danish nationwide patient database, which allows for broad generalizability within Denmark. On the other hand, Etminan et al. (2019) collected data from a health claims database, potentially limiting generalizability to populations with private health insurance. The first study included two fluoroquinolones, ciprofloxacin and moxifloxacin, whereas the latest study also included levofloxacin and gemifloxacin.

Additionally, different antibiotics were employed to compare their effect to fluoroquinolones. Strange et al. (2021) conducted a study comparing the effect of fluoroquinolones with penicillin V, amoxicillin, and macrolides. In contrast, Etminan et al. (2019) included only two antibiotics as a non-fluoroquinolones group, amoxicillin and azithromycin. In addition, Strange et al. (2021) evaluated risks following fluoroquinolone exposure within 30 days, 90 days, and one year prior to the event, while Etminan et al. (2019) assessed risk within 30, 60, and 365 days.

Despite these methodological differences, both studies shared the nested case-control design. Cases and controls were selected from the same database, which is more likely to reduce selection bias compared to traditional case-control studies that often select participants by using convenience sampling (Ernster, 1994; Sedgwick, 2014).

There were several limitations in this systematic review and meta-analysis, one being that it is based on the available data, which might be insufficient in terms of depth or breadth. Another limitation was missing information from relevant studies due to including only English and Thai studies. Furthermore, while the study searches were performed as broadly as possible within the limited time, the number of articles relating to the association between fluoroquinolones and mitral and aortic regurgitation was indeed small. By focusing on database selection, performing search in HITAP is inappropriate, due to the objective of this study was to focus on the adverse effect. Furthermore, thesis databases

were limited to Silpakorn University and Chulalongkorn University, which may result in the possibility of missing relevant studies and increasing the chance of publication bias.

Conducting a systematic review and meta-analysis rather than developing new research to gather original data has several advantages. Secondary data analysis provides information that is larger and of higher quality than the data collected by individual researchers. By combining primary studies with varying sample sizes and patient populations, this research methodology can enhance the generalizability and transferability of relevant research results (Greenhoot & Dowsett, 2012; Lee, 2019; Windle, 2010).

4. CONCLUSION

This research method provides a more reliable estimation of the association between fluoroquinolone exposure and the risk of mitral and aortic regurgitation, showing that fluoroquinolones are not associated with an increased risk of these conditions. The findings from this study contribute to the existing body of knowledge and provide valuable evidence to support clinical decision-making regarding the use of fluoroquinolones in medical practice. This information can assist healthcare professionals in making informed choices when considering fluoroquinolones as a treatment option.

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