Comparative Cardiovascular Efficacy & Safety of NSAIDs: ***A Systematic Review and Meta-analysis of Randomized Controlled Trials***

Abstract

NSAIDs, or nonsteroidal anti-inflammatory medications, are popular and efficient analgesis and frequent mainstay treatements for inflammatory disorders. However, their cardiovascular safety is questionable. The aims of the current study were: (1) to evaluate the comparative cardiovascular efficacy of NSAIDs; (2) to investigate the cardiovascular safety and risks associated with NSAID use; (3) to highlight the importance of alternative therapies for patients who display contraindications to NSAID. A number of digital databases were explored to retrieve relevant studies. These consist of ClinicalTrials.gov, PubMed, Google Scholar, ScienceDirect, etc. The final sample consisted of 17 primary studies.A total of 12/17 (71%) studies advocated the efficacy and safety of NSAIDs. The remaining 2/17 (11%) showed that there was no discernible difference between the NSAID and non-NSAID groups in terms of mortality, cardio-respiratory morbidity, and cardiovascular risk. A forest plot was created using data from eight distinct studies. The results for the incidence of cardiovascular events were found to be statistically significant. The heterogeneity was calculated to be Tau2= 0.15; Chi2=117.67; df=6; I2=95%. The overall effect size was found to be Z=0.08 ($p<0.94$); the Hazard Ratio was found to be 0.84, CI=95% (CI, 0.72 = 0.98). Certain agents have a higher risk of causing unfavorable cardiovascular events, although other agents might have a safer profile. Clinicians must have this comprehensive knowledge to balance the therapeutic benefits of NSAIDs with any potential cardiovascular hazards when making judgments.

Keywords: *Non-steroidal anti-inflammatory drugs, NSAIDs, cardiovascular medications, COX inhibitors, MI, Stroke, Atrial Fibrillation, Randomized Control Trials*

Abbreviations:
NSAIDs - Non-steroidal anti-inflammatory drugs
COX2 - Cyclooxygenase 2
APPROVE - Adenomatous Polyp Prevention on Vioxx
PICOS - Population, Intervention, Comparison, Outcomes, Study design
PRISMA - Preferred Reporting Items for Systematic Review and Meta-analysis
RE-LY - Randomized Evaluation of Long Term Anticoagulant Therapy Trial

ARISTOTLE - Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation
SPAQ - Sleep and Pain Activity Questionnaire
CABG - Coronary Artery Bypass Graft

Introduction

NSAIDs, or nonsteroidal anti-inflammatory medications, are popular and efficient analgesics [1]. Their cardiovascular safety has received a lot of attention over the last 20 years. Since cardiovascular disorders are a major source of morbidity and death, it is essential to clarify the unique risk profiles associated with each NSAID in order to support evidence-based therapeutic decisions. It is important to evaluate their relative efficacy in cardiovascular safety given their widespread use worldwide. NSAIDs exert their effect by reducing prostaglandin synthesis via the inhibition of the enzyme cyclooxygenase. Classical NSAIDs, such as diclofenac and ibuprofen, have been associated with gastrointestinal adverse effects [2][3]. The most significant risk of negative vascular consequences has been linked to selective cyclooxygenase 2 (COX2) inhibitors, or coxibs.

The gastrointestinal safety of rofecoxib and naproxen was investigated in the VIGOR trial (Vioxx Gastrointestinal Outcomes Research), which discovered a 2.38-fold increased risk of cardiovascular events (myocardial infarction, stroke, and cardiovascular death) for rofecoxib[4]. According to recent data, NSAIDs have a worse CV profile, COX-2 selective medications are safer for the GI system. Naproxen, on the other hand, is one of the NSAIDs with the worst GI toxicity, although appearing to be safer for the heart [5]. However, non-selective NSAIDs, particularly those with potent COX2 inhibition like diclofenac, are also a cause for concern.NSAID use has been linked to an elevated risk of thrombotic cardiovascular events, especially for short-term usage (less than seven days). While it is not recommended for people with cardiovascular disease to take NSAIDs, painkillers are often necessary, and when safer alternatives are not available, NSAIDs are commonly prescribed for pain treatment. NSAIDs are the mainstay treatment regimens of inflammatory disorders, such as gouty arthritis, osteoarthritis, gout, IBD, etc. The main therapeutic options for an acute flare of these conditions are colchicine, non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids [6]. Based on additional examination of a recent study, the incidence of thrombotic cardiovascular events in etoricoxib-using individuals with arthritis is comparable to that of diclofenac-using people who use these medications for an extended period of time [7]. This study aimed to analyze NSAID-associated cardiovascular risk, including both coxibs and classical NSAIDs, by conducting a meta-analysis of randomized controlled trials.

Rationale

According to recent literature, NSAIDs are an effective pharmacological strategy to treat and prevent inflammatory and bleeding disorders. However, the associated side-effects and cardiovascular risks are also well-documented. We investigated the benefits and potential side-effects of NSAIDs use within primary studies, i.e. randomized controlled trials to have deeper insights into the accuracy of treatments. The current study, thus, weighs the benefits and drawbacks of NSAIDs to fill in the literature gap. This study will help the clinical practitioners and medical researchers to devise more effective and improved treatment regimens for the indications that require NSAID use.

Objectives

The objectives of the current study are: (1) to evaluate the comparative cardiovascular efficacy of NSAIDs; (2) to investigate the cardiovascular safety and risks associated with NSAID use; (3) to highlight the importance of alternative therapies for patients who display contraindications to NSAID use; (4) to assess the most effective NSAID from with-in the drug group (Celecoxib, Aspirin, Etoroxib, etc).

Definition

-cardiovascular efficacy: cardiovascular efficacy of a drug refers to the ability of the drug to reach the therapeutic objectives benchmark with the recommended dosing regimen. In cardiovascular terms, it means the ability of a drug to reduce the overall incidence of cardiovascular events from occurring. It includes myocardial infarction (MI), thromboembolic stroke, Intracranial bleed (ICB), hemorrhagic stroke, Upper or lower GI bleed, Cardiovascular-related mortality, or mortality due to any cause (all-cause mortality). The incidence rate is frequently interchangeable with “frequency of events”, “rate of mortality.”

-cardiovascular safety: cardiovascular safety of a drug refers to the ability of the drug to improve the quality of life (QOL) outcomes of a patient. This signifies the drug’s ability to lower the overall mortality; improved patient satisfaction post-treatment; decrease in the occurrence of adverse events (bleeding events); decrease in overall complications, or improvement in quality of life scores through 5-year survival, or recurrence of cardiovascular events.

-cardiovascular risks associated with NSAIDs: Adenomatous Polyp Prevention on Vioxx (APPROVe) trial findings on rofecoxib's detrimental effects on cardiovascular disease (CVD) ultimately resulted in the drug's withdrawal in a number of nations [8]. Compared to naproxen, rofecoxib has been linked to an increased risk of thromboembolic events [9].Rofecoxib was linked to renal problems and cardiac arrhythmias in another investigation [10]. Nonetheless, individuals receiving treatment with other COX-2 inhibitors did not experience comparable side effects. More significantly, it has also been demonstrated that a number of nonselective NSAIDs, such as naproxen and ibuprofen, and other semiselective NSAIDs, such as diclofenac and

meloxicam, raise the rates of CVD, discomfort, osteoarthritis, rheumatoid arthritis, musculoskeletal diseases, and additional concomitant problems.

Methodology

Eligibility Criteria

We set the eligibility criteria according to 'Population, Intervention, Comparison, Outcome, and Study Design (PICOS)' scheme, as recommended by PRISMA guidelines.

-***inclusion*** criterion was: (1) Literature that was published from 2018-2023; (2) Adults who had an active NSID prescription due to a pre-existing condition (3) Studies investigating various dose-related therapeutic impact of NSAIDs; (4) Studies comparing NSAIDs with other non-steroidaalantiinflammatory drugs. (5) Studies reporting efficacy in prevention and safety outcomes (bleeding events); (6) Controlled study designs that consisted only Randomized Control Trials.

-***exclusion*** criterion was: (1) Any study published before 2018; (2) Non-observational studies and other review studies were not selected; (3) The studies with a target population of diagnoses other than Osteoarthritis, Gout, and Inflammatory disorders (4) Studies which included young pediatric population.

Information Sources

A number of digital databases were explored to retrieve relevant studies. These consist of ClinicalTrials.gov, PubMed, Google Scholar, ScienceDirect, Medline, Embase, and so forth. There were also independent journals and other sources included. Other than databases, the literature was sourced from publications like the "Journal of Cardiovascular Pharmacology and Therapeutics," "JAMA Network," "Journal of American College of Cardiology," "Elsevier," "European Heart Journal," and others.

Search Strategy

The search strategy was established on the basis of PICOS scheme (discussed later) and it was aimed at retrieving only the most relevant data from the digital databases. In the current search strategy, a total of 17 studies (out of a total sample of n=73) were eligible. We conducted a comprehensive review of the literature, and covered the terms: " ("Non-Steroidal Anti-Inflammatory Agents"[Mesh] OR "NSAIDs"[Mesh] OR "Nonsteroidal Anti-Inflammatory Drugs" OR "NSAID") AND ("Cardiovascular Diseases"[Mesh] OR "Myocardial Infarction"[Mesh] OR "Stroke"[Mesh] OR "Cardiovascular System"[Mesh] OR "Hypertension"[Mesh] OR "Risk Assessment"[Mesh] OR "Comparative Study"[Mesh]) AND ("Cardiovascular safety" OR "Cardiovascular risk" OR "Myocardial infarction" OR "Stroke" OR "Hypertension" OR "Comparative analysis") AND Humans[Mesh] Filters: Randomized Controlled Trial, from 2017 - 2023". Further, we inspected the reference list of the studies that were selected in the final sample.

Selection Process

Three researchers searched for evidence that met the inclusion criteria in peer-reviewed journals and publications. To reduce the likelihood of publication bias, a thorough selection of the literature lead to an investigation of peer-reviewed journals with a high impact factor. All selected studies were uploaded to the screening application Rayyan.ai for screening of primary and secondary literature [47]. Three researchers worked together to "include" or "exclude" relevant papers depending on the inclusion and exclusion criteria. A total of 17 papers (n =73) were considered for the final review and analysis. Research that did not meet the screening eligibility conditions was labeled as "dispute" or "exclusion." We assembled a team of three researchers to select studies and serve as tiebreakers for a contested study. Studies that (1) had a different population (2) with a design and methodology that was not appropriate inclusion, (3) calculated incorrect outcomes, or (4) had a high risk of bias was all excluded. Occasionally, there was a combined effect from several exclusionary factors.

Data Items

Following the completion of the secondary screening protocol, the total sample size (n=21) for th e chosen literature was evaluated.For the chosen studies from journals and other independent res ources (if the reports were available), we created a PRISMA flow diagram using the Preferred Re porting Items for Systematic Review and Meta-Analysis (PRISMA) standards [11]. (figure 1)

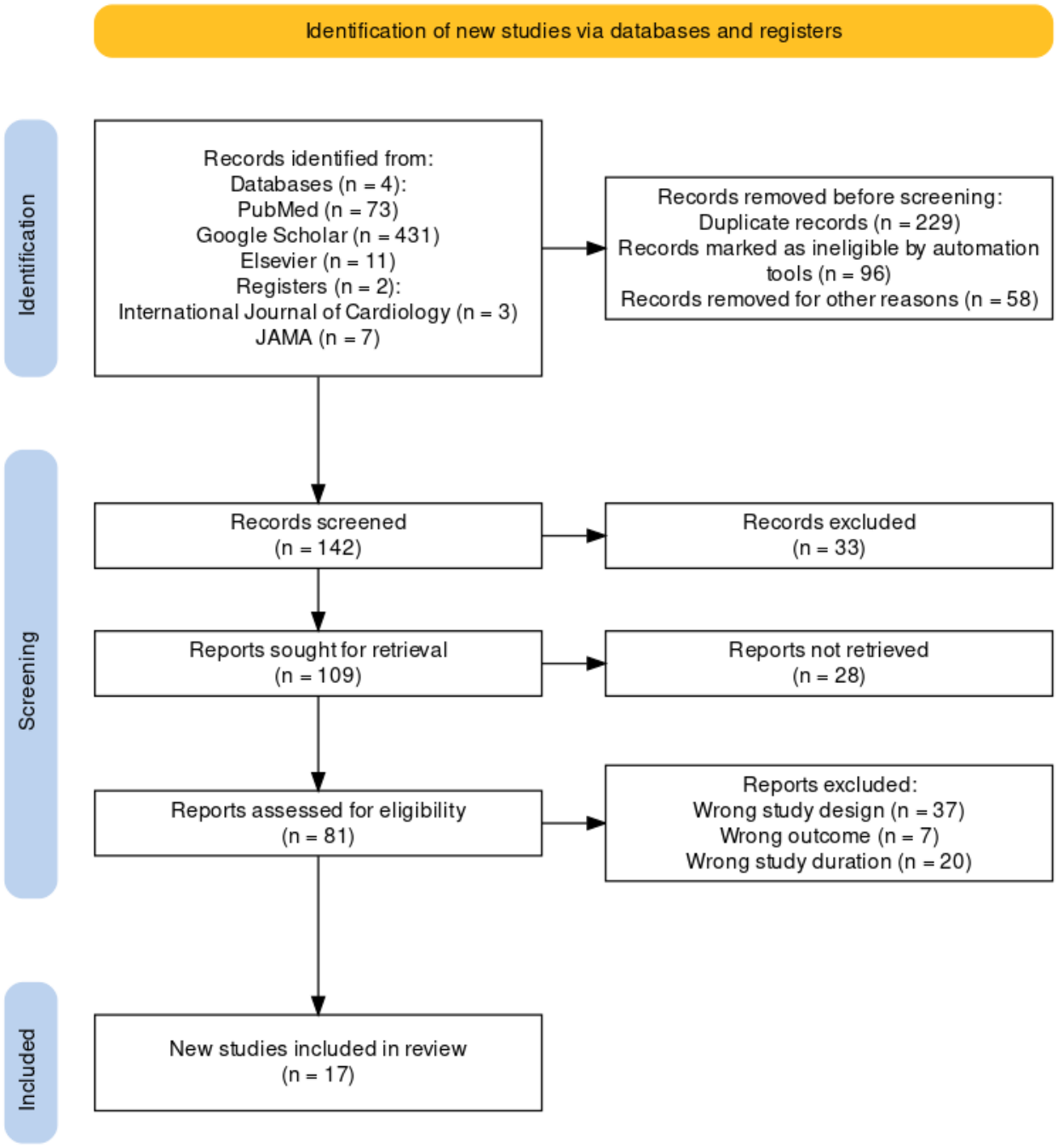

Figure 1: PRISMA Flow Diagram for selected studies

To reduce bias in the analysis, the following measures were taken: (1) choosing high-quality research; (3) requiring peer reviewers to disclose conflicts of interest; and (5) substituting meta-analyses for regular review articles. Systematic reviews and narrative reviews were excluded in order to maintain the study's standards. Following the stages of removing publication bias

proposed by Chalmers et al. (1990), these guidelines identify and eliminate bias from the study protocol [12]. Based on this data, a "traffic light" figure was generated through randomization.

Assessment of Research Quality

- *meta-analysis:* In order to evaluate 'bias' in the studies that were chosen, we looked for digital and online tools. With the exception of randomized control trials (RCTs), every study was evaluated using an online tool in order to produce a quality assessment table for every study that was a part of the meta-analysis. Table 2 (the assessment table for the five studies) is mentioned below. Additionally, every primary study—that is, all RCTs that qualified for analysis—was chosen on its own using the Cochrane criteria for risk of bias (ROB). (Higgins & Associates, 2011). The domains with potential for bias were [13] (1) random sequence generation; (2) allocation concealment; (3) participant and personnel blinding; (4) outcome assessment blinding; (5) incomplete outcome data (attrition bias); (6) selective reporting (reporting bias); and (7) other biases. For the statistical meta, data that was continuous was taken from eight of the twenty-one primary studies. For the meta-analysis, we used Review Manager (RevMan version 5.4) to create a "forest plot." Rev-man (version 3.5.1) was used to conduct a meta-analysis of eight primary studies (study design = Randomized Control Trials). For the analytical tool, three researchers gathered comparable and pool-able data [14]. Every piece of information was accessible as continuous variables. The results section of our study contains the meta-analysis's data.

Results

Study Characteristics

A total of 17 primary studies (n=73) were selected after tertiary screening. All the selected studies were controlled trials, conuducted between 2018 and 2023. The sample sizes for the studies ranged from n=62 to n=15834. Follow up data points ranged from 3 weeks to 48 months. A total of 12/17 (71%) studies advocated the efficacy and safety of NSAIDs. These concluded that NSAIDs significantly reduced the risk of major and non-major bleeding events in a majority of cohorts. We concluded that there was a "negative association" between NSAID use and cardiovascular safety. 3/17 studies (18%) were against the null hypothesis. These concluded that concomitant as well as solo-therapy with NSAIDs increases mortality, increases recurrence, and increases the risk of hospitalization, and major S/E (Systemic/ Embolic) stroke. The remaining 2/17 (11%) showed that there was no discernible difference between the NSAID and non-NSAID groups in terms of mortality, cardio-respiratory morbidity, and cardiovascular risk. We concluded that there was "no effect" for the comparative data pool from these studies. The results of the systematic review are given in the table below (Table 1):

Table 1: Results of the Systematic Review

Sr	Study ID	Origin	Study Design	Participants	Interventions	Key findings

1	Gaziano JM et al. 2018 [15]	NA	Randomised, double-blind, placebo-controlled trial	12546 individuals (placebo=6276; aspirin=6270) with moderate cardiovascular risk were 55 years of age or older in males and 60 years of women.	Using a computer-generated randomization code, patients were randomly assigned (1:1) to receive enteric-coated aspirin (100 mg) or placebo pills once a day.	The aspirin group had 269 (4·29%) patients meet the primary endpoint, while the placebo group had 281 (4·48%) patients (hazard ratio [HR] 0·96; 95% CI 0·81–1·13; p=0·6038).
2	Ruschitzka F et al. 2017 [16]	USA	double-blind, randomized, multicentre non-inferiority CV-safety trial,	444 individuals with osteoarthritis (92%) or rheumatoid arthritis (8%), with a mean age of 62 ± 10 years and 54% female.	In a 1:1:1:1 allocation, the effects of celecoxib (100–200 mg bid), ibuprofen (600–800 mg tid), or naproxen (375–500 mg bid) were evaluated on 24-hour ambulatory blood pressure after four months.	Following these modifications, there was a difference of -3.9 mmHg (P = 0.0009) between ibuprofen and celecoxib, -1.8 mmHg (P = 0.12) between naproxen and celecoxib, and -2.1 mmHg (P = 0.08) between naproxen and ibuprofen.
3	Kent AP et al. 2018 [17]		RE-LY (Randomized Evaluation of Long Term Anticoagulant Therapy) trial	2,279 patients in the 18,113 participants in the RE-LY study took NSAIDs at least once while they were in the experiment.	The RE-LY trial compared patients who never took NSAIDs during the trial (n ¼ 15,834) with the group of patients who used nonselective NSAIDs at least once (n ¼ 2,279).	NSAID was linked to a higher risk of hospitalization, stroke/SE, and significant bleeding. In comparison to warfarin, DE 150 and 110 mg b.i.d. remained safe and effective.
4	Obeid S et al. 2022 [18]		Prospective Randomized Evaluation of Celecoxib Integrated Safety vs. Ibuprofen Or Naproxen Trial	24081 participants who required NSAIDs for osteoarthritis or rheumatoid arthritis (RA)	The pre-specified composite cardiorenal outcome (adjudicated renal event, hospitalization for congestive heart failure, or hospitalization for hypertension) was evaluated in the	Celecoxib had a trend toward lower risk when compared to naproxen (HR 0.79, CI 0.61–1.00, P = 0.058) and a considerably lower risk when compared to ibuprofen [hazard ratio (HR) 0.67,

					current study for its occurrence, severity, and NSAID-related risk.	confidence interval (CI) 0.53–0.85, P = 0.001).
5	Brito F et al. 2017 [19]		retrospective analysis of data from 2 RCTs	A total of 5887 patients were studied. Median age was 65 years, 78% were male, and 91% were White. NSAIDs were used in 2368 (40.2%) patients.	combined information from two multicenter RCTs (MEND-CABG II [n = 3023] and PREVENT IV [n = 3014])	After coronary artery bypass graft surgery, NSAIDs were taken by most patients (1822 [30.9%]); 289 (4.9%) used them both before and after the procedure, and 257 (4.4) only received them before.
6	Dalgaard F et al. 2020 [20]		The ARISTOTLE trial	ARISTOTLE trial (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; n=18 201)	The study examined the effects of warfarin with apixaban in patients with atrial fibrillation who were at higher risk of stroke. NSAID use at baseline, incident NSAID use during the trial, and never users were reported.	NSAID use during an incident was linked to major and nonmajor bleeding that was clinically significant, but not to gastrointestinal bleeding.
7	Solomon DH et al. 2019 [21]		randomized controlled trial	Patients were divided into derivation and validation cohorts.	Patients were randomized to receive celecoxib, naproxen, or ibuprofen at typical dosages.	The cardiovascular safety was in the order: Celecoxib >Naproxexn>Ibuprofe. However, the results changed significantly when co-morbids were introduced and high-diosing regimens were considered.

8	Reed GW et al. 2018 [22]		randomized controlled trial	Trial included 23,953 patients with osteoarthritis or rheumatoid arthritis at increased cardiovascular risk randomized to celecoxib, ibuprofen, or naproxen.	An analysis of the PRECISION trial (Prospective Randomized Assessment of Celecoxib Integrated Safety in Comparison with Ibuprofen or Naproxen)	When used without aspirin, naproxen or ibuprofen exhibited a higher risk for the primary composite endpoint in comparison to celecoxib (hazard ratio [HR]: 1.81; 95% CI: 1.46 to 2.26; p <0.001, and HR: 1.52; 95% confidence interval [CI]: 1.22 to 1.90, p <0.001, respectively).
9	Chan FKL et al. 2017 [23]	Hong Kong	industry-independent, double-blind, double-dummy, randomized trial	We enrolled 514 patients between May 24, 2005, and November 28, 2012; 257 patients were assigned to each research group, and all patients were part of the intention-to-treat population.	Using a computer-generated list of random numbers, patients who tested negative for Helicobacter pylori were randomly assigned (1:1) to receive oral administrations of either celecoxib 100 mg twice daily plus esomeprazole 20 mg once daily or naproxen 500 mg twice daily plus esomeprazole 20 mg once daily for a period of 18 months.	Celecoxib + proton-pump inhibitor is the recommended treatment to lower the risk of recurrent upper gastrointestinal bleeding in patients who require concurrent aspirin and NSAID due to their high risk of both cardiovascular and gastrointestinal problems.
10	Balachander B et al. 2018 [24]	India	randomized clinical trial	146 infants were admitted to the tertiary care newborn hospital between October 2014 and January 2016; these included	The echocardiography was done 24 hours after completion of treatment by a cardiologist blinded to treatment.	There was no discernible difference between the two groups in terms of mortality, cardio-respiratory morbidity, or PDA closure (RR 0.97, 95%CI 0.78–1.20, p = 1).

				preterm neonates who had an echo confirmation of hemodynamically severe PDA.		
11	Solomon DH et al. 2018 [25]		PRECISION trial; double-blind randomized controlled trial	A total of 24,081 patients with OA or RA who had a moderate or high risk for CV disease	Interventions comprised 600–800 mg of ibuprofen three times a day, 375–500 mg of naproxen twice a day, or 100–200 mg of celecoxib twice a day.	The risk of a major adverse CV event was significantly reduced when celecoxib was compared with ibuprofen
12	Dalewski B et al. 2019 [26]		Randomized controlled clinical trial (RCT)	52	Visual Analogue Scale (VAS) and Sleep and Pain Activity Questionnaire (SPAQ) were used twice, once at the start of the study and again after three weeks. Occlusal appliance (OA) with nonsteroidal anti-inflammatory drug (NSAID) therapy (nimesulide), occlusal appliance with dry needling (DN), and occlusal appliance (OA-control group).	Answers to questions 7, 8, and 9 in the NSAID group (M1) and the DN group (M2) revealed significantly different answers only to questions 7 and 9, when comparing pretreatment and posttreatment responses.
13	Motov S et al. 2019 [27]		A Randomized Controlled Trial	We enrolled 225 subjects (75 per group); in adult ED patients with acute painful conditions.	comparing the analgesic efficacy of 3 doses of oral ibuprofen (400, 600, and 800 mg) in adult ED	Oral ibuprofen administered at doses of 400, 600, and 800 mg has similar analgesic efficacy for short-

					patients	term pain relief in adult patients presenting to the ED with acute pain.
14	Akinbade AO et al. 2018 [28]		double blind randomized controlled trial	Postoperative pain intensity was self-recorded by subjects at 4, 8, 16, 24 and 48 hours after extraction, using visual analogue scale (VAS)	Data analysis involved descriptive statistics, 2-sample Wilcoxon Mann–Whitney U, and Kruskal Wallis rank tests. The mean VAS score of the celecoxib group (32.35± SD 23.96) at 4 hours	The Celecoxib group also had the lowest mean VAS scores at 8 hours, 24 hours, and 48 hours after the extraction. The mean VAS score of the celecoxib group (32.35± SD 23.96) at 4 hours was the lowest among the three groups.
15	Yeomans ND et al. 2018 [29]		randomized, double-blind controlled trial	24 081 patients. Osteoarthritis or rheumatoid arthritis patients, needing ongoing NSAID treatment; follow-up durations were 20.3 and 34.1 months.	Assigned at random to receive low-dose aspirin or corticosteroids if previously prescribed, celecoxib 100–200 mg b.d., ibuprofen 600–800 mg t.d.s., or naproxen 375–500 mg b.d. in addition to esomeprazole.	Rarely do NSAIDs combined esomeprazole cause clinically severe gastrointestinal problems in individuals with arthritis. Celecoxib had superior general GI safety when co-prescribed with esomeprazole compared to ibuprofen or naproxen.
16	Diercks GR et al. 2019 [30]		multicenter, randomized, double-blind noninferiority trial	A total of 1832 kids were evaluated for eligibility; 741 kids were enrolled, 688 kids (92.8%); 366 boys [53.2%] were given the study; the kids were between the	Participants were randomized to receive ibuprofen, 10 mg/kg (n = 372), or acetaminophen, 15 mg/kg (n = 369), every 6 hours for the first 9 postoperative days.	In the acetaminophen group, the rate of bleeding that required surgical intervention was 1.2%, while in the ibuprofen group, it was 2.9% (difference, 1.7%; 97.5% CI upper limit, 3.8%; P =.12

				ages of 2 and 18 and had tonsillectomy.		for noninferiority).
17	Waraich HS et al. 2018 [31]	India	a prospective, open-label, parallel trial	80 patients out of 102 screened for osteoarthritis in the Department of Orthopaedics, Guru Nanak Dev Hospital	Group A patients received Tab etoricoxib 60 mg once daily and Group B patients received Tab. Aceclofenac 100mg twice daily. Patients were followed up after three weeks and at six weeks	It was discovered that the indications and symptoms of osteoarthritis were significantly improved in both groups. On the other hand, aceclofenac outperformed etoricoxib in terms of changes in the osteoarthritic severity index, the visual analogue scale score, and the overall evaluation of patients and doctors.

Risk of Bias Plot

As was previously indicated, each study that was incorporated into the meta-analysis had its risk of bias evaluated. In the end, the final sample consisted only of the studies that demonstrated a "low" risk of bias across all domains. For the final evaluation, a "traffic lights" plot was made using the Cochrane ROBv2 tool. The figure below (Fig. 2) displays the ROB plot for seven primary studies.

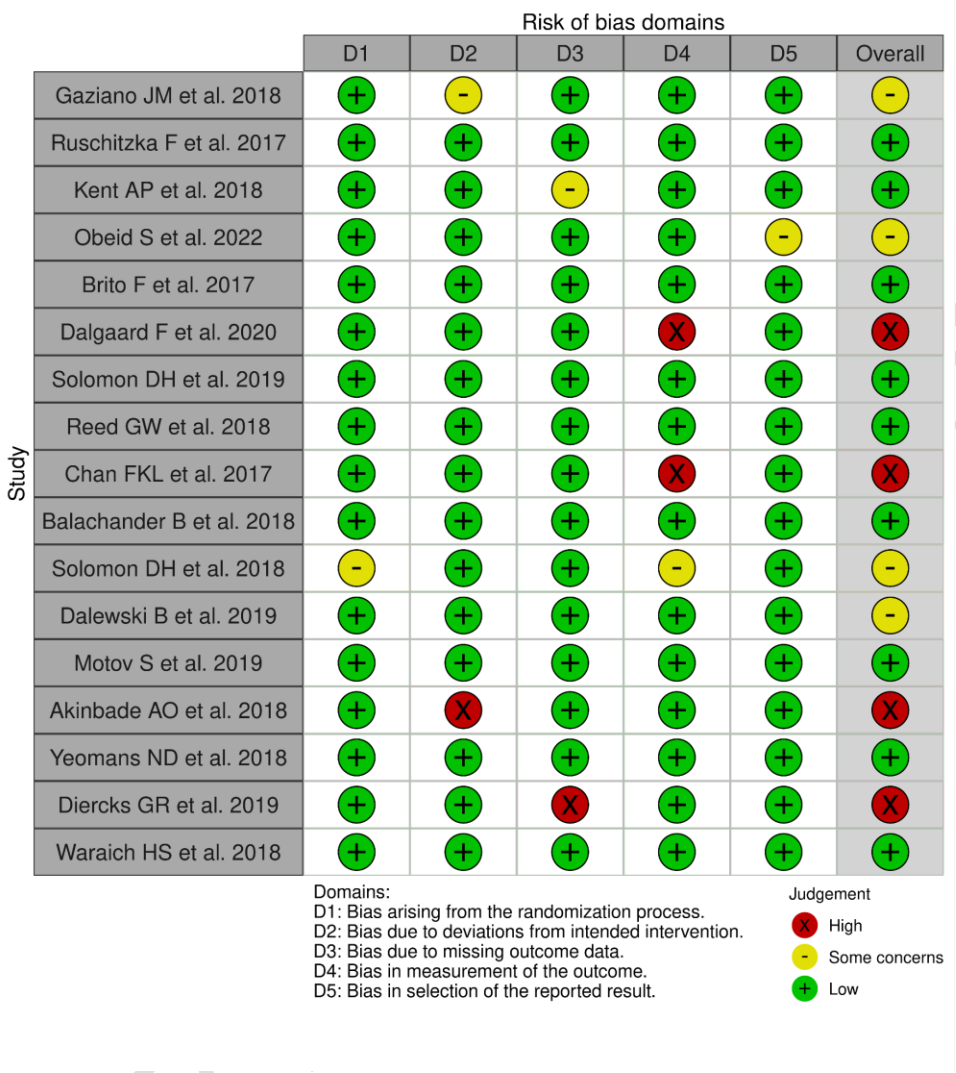

Figure 2: Cochrane ROB plot for all randomized control trials

Forest Plots

Incidence of Cardiovascular Events

To compute the hazard ratio (HR) in terms of "log[HR]" and Standard Error "(SE)," a random-effects model was selected. The horizontal axis was used to calculate the Confidence Interval (CI=95%), and the plot's "point estimation" was presented as green squares. There was no significant change in the total sample size (n = 62, 46, 146, 15834, 6270) between the control groups. The vertical line in the center denotes a condition of "no effect." The individual effect for the current analysis was found to be statistically significant for 5/7 studies, (Brito F et al., 2017) (Dalewski B et al., 2018) (Gaziano JM et al., 2018) (Obeid S et al., 2018) (Solomon DH et al., 2018). The heterogeneity was calculated to be Tau2= 0.15; Chi2=117.67; df=6; I2=95%. The overall effect size was found to be Z=0.08 (p<0.94); the Hazard Ratio was found to be 0.84, CI=95% (CI, 0.72 = 0.98). On the other hand, the individual effect size for 2/7 studies (Reed GW wt al., 2018) (Kent AP et al., 2018) was found to be “negative’. From the current analysis, we concluded that NSAIDs were significantly more efficaious and provided a greater sagety index in lowering the overall incidence of cardiovascular events, such as MI, Stroke, ICB, and other

non-major bleeding events, for example, GI bleeding. However, the results of the analysis were statistically limited. The forest plot for the meta-analysis is shown in the figure below (fig 3):

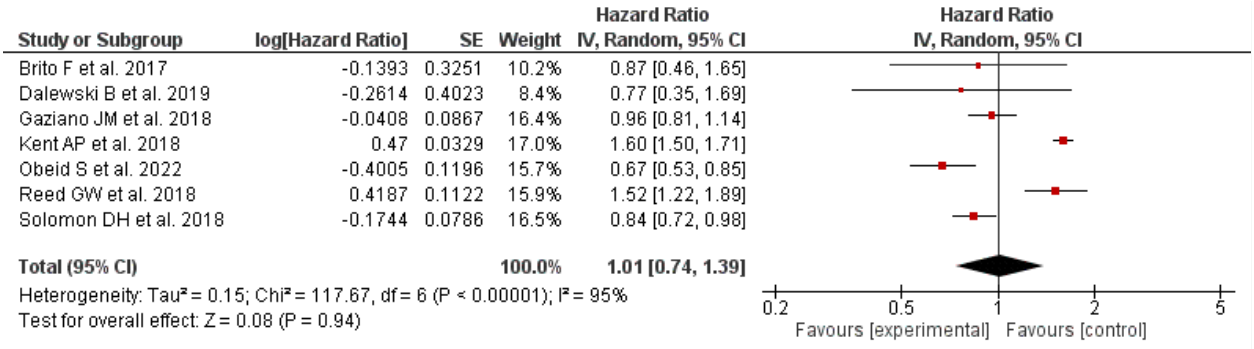

Fig 3: Forest plot for Incidence of Cardiovascular Events [26] [25][22][19][18][17][15]

Incidence of GI Bleeding

The incidence of Gastrointestinal bleeding was considered as another safety outcome in the current study. 4/17 studies showed comparable and pool-able data for the studied outcome. The results of the current analysis showed a clinical;y significant reductIon in the incidence and frequency of fatal and non-fatal gastrointestinal bleeding events after NSAID use. These bleeds were caused as a results of gastric ulcers, peptic ulcer disease (PUD), Helocobacter Pylori (H. Pylori) infection, and other non-coaguable blood states that increase the risk of GI bleeding. The individual effect of all the studies (4/17)(Chan FKL et al., 2017) (Diercks GR et al., 2019) (Solomon DH et al., 2018) (Yeomans ND et al., 2018) showed a positive association between NSAID therapy and safety in prevention and treatment of acute and chronic GI bleeding states. The avaraged values for hazard ratIo was found to be HR=0.43 (95% CI, (0.27 - 0.68)). The overall effect size was found to be statistically significant; Z=4.89 (p<0.001). The heterogeneity was found to be Tau2=0.01; Chi2=3.67; df=3; I2=18%. The forest plot for the studies is given in the figure below (fig 5):

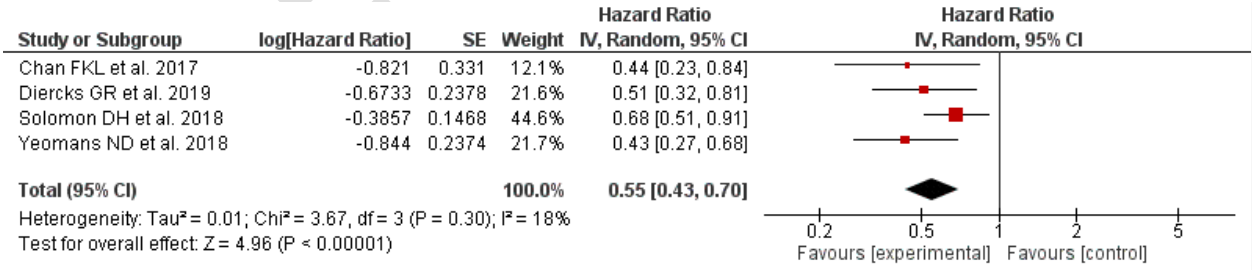

Figure 4: Forest plot showing Incidence of GI Bleeding [30][29][25][23]

All-cause mortality

All-cause mortality (death due to any cause) was considered as the secondary outcome in the current study. Long-term QOL outcomes also include death due to any cause after NSAID use. 3 studies (Gaziano JM et al., 2018) (Kent AP et al., 2018) (Obeid S ete al., 2022) showed

significant scores for all-cause mortality in all pre-treatment and post-treatment analyses. The individual effect sizes for ⅔ studies showed a positive assiciation between NSAID use and improvement in mortality scores in all-cause mortality indices. The overall effect size was found to be Z=0.41, (p=0.68). The hetergeniety in the data was found to be: Chi2=8.51, df=2; I2=77%. ⅓ studies (Obeid S et al., 2022) showed a "negative' association between all-cause mortality scores and NSAID use. We concluded that NSAID can reduce all-cause mortality in patients with no other pre-existing comorbidities.

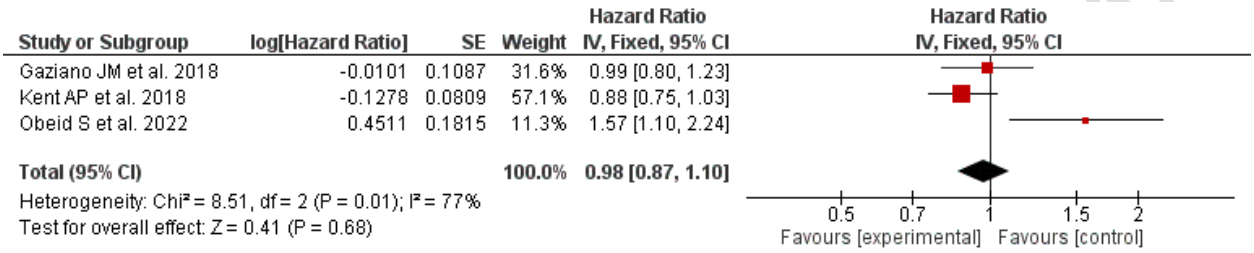

Figure 5: Forest plot for All-cause Mortality [18][17][15]

Discussion

Non-steroidal anti-inflammatory drugs (NSAIDs) have a complex safety profile that should be carefully considered while using them in the cardiovascular system. NSAIDs reduce inflammation and pain by blocking the activity of cyclooxygenase enzymes. This method may have consequences for the cardiovascular system, though. The suppression of prostaglandin synthesis, which is protective and helps to maintain vascular homeostasis, raises questions.Certain nonsteroidal anti-inflammatory drugs (NSAIDs), particularly those that inhibit cyclooxygenase-1 and -2, have been associated with an increased risk of severe cardiovascular events, including myocardial infarction and stroke. Hypertension, fluid retention, and compromised renal function are further considerations [32]. The relative cardiovascular safety of NSAID use is a major source of worry, particularly for those with or at risk for cardiovascular disease [33]. Until recently, the corpus of data was limited to prior research with small sample sizes. The overwhelming body of research indicates that NSAID use is not recommended for those who have cardiovascular disease or are at high risk of developing it [34]. The lowest effective and shortest-lasting NSAID doses should be administered because the risk changes with duration and dose, according to the findings. A similar meta-analysis, conducted by Arias LHM et al. (2018) [35], showed that NSAIDs as a pharmacologic class present an increased CVR vs no anti-inflammatory treatment (RR, 1.24 [1.19-1.28]). The findings of our study suggest the incidence of cardiovascular events significantly decrease after NSAID therapy. For example, the study conducted by Gaziano JM et al., 2018 [15] investigated the effectiveness of NSAID (Aspirin) given in the 100mg daily dose for diagnosed cases of Osteoarthritis (OA). The aspirin group had 269 (4·29%) patients meet the primary endpoint, while the placebo group had 281 (4·48%) patients. The primary endpoint was taken to be the occurrence of major or non-major cardiovascular events after NSAID use. The study conducted by Dalgard F et al., 2020 via the

data from the ARISTOTLE trial examined the effects of warfarin with apixaban in patients with atrial fibrillation who were at higher risk of stroke [20]. NSAID use during an incident was linked to major and nonmajor bleeding that was clinically significant, but not to gastrointestinal bleeding. On the other hand, the trial conuducted by Balachander B et al. 2018 enrolled 146 infants were admitted to the tertiary care newborn hospital between October 2014 and January 2016; these included preterm neonates who had an echo confirmation of hemodynamically severe PDA. The study showed no discernable difference between cardio-respiratory safety, cardiovascular risk, and hemodynamic severity of the patients in PDA. The retrospective analysis of the data conducted by Brito F et al., 2020 showed that after coronary artery bypass graft surgery (CABG), NSAIDs were taken by most patients (1822 [30.9%]); 289 (4.9%) used them both before and after the procedure.

GI Impact

NSAIDs have the potential to harm the gastrointestinal system's upper and lower parts. Thirty to fifty percent of individuals taking NSAIDs have upper gastrointestinal lesions, while up to seventy percent of chronic NSAID users have small-bowel injury, with erosions and ulcers occurring in thirty to forty percent of cases. The majority of these lesions have no clinical importance, however as compared to non-users, the risk of peptic ulcer complications is four times higher [5]. The GI impact of NSAIDs was also assessed from with-in drug group efficacies. According to a study conducted by Solomon DH et al. 2018, Celecoxib had superior general GI safety when co-prescribed with esomeprazole compared to ibuprofen or naproxen. In another study by Yeomans ND et al. 2018, NSAIDs combined esomeprazole only rarely caused clinically severe gastrointestinal problems in individuals with arthritis.

Within-group Comparative Efficacies

After the relative safety of NSAIDs was ascertained, we also investigated the comparative efficacies of NSAIDs within the group. These included Ibuprofen, Naproxen, Diclofenec, and Celecoxib. The study conducted by Motoc S et al., 2019 showed that Oral ibuprofen administered at doses of 400, 600, and 800 mg has similar analgesic efficacy for short-term pain relief in adult patients presenting to the emergency department with acute pain. In another study by Solomon DG et al., 2018, the cardiovascular safety was in the order: Celecoxib >Naproxexn>Ibuprofe. However, the results changed significantly when co-morbids were introduced and high-diosing regimens were considered. Further, it was also assessed that Celecoxib was better tolerated when given in conjunction with Proton pump inhibitors (PPIs), such as omeprazole and esomeprazole.

Limitations

The current study had few limitations. Firstly, the meta-analysis from the randomized trials analysed relatively small sample sizes. The sample sizes taken for meta-analysis could not be standardized according to usual protocols. We used study characteristics in consideration but did not consider methodological characteristics of studies. Secondly, very few primary studies were

utilized to assess the effectiveness and safety (outcome domain) for such a large sample size. Thirdly, we evaluated the overall combined effect of all sample sizes, but within group and sub-group analyses were not performed

Conclusion

Individual NSAIDs have different risk profiles, particularly for individuals with underlying cardiovascular problems. Certain agents have a higher risk of causing unfavorable cardiovascular events, although other agents might have a safer profile. Clinicians must have this comprehensive knowledge to balance the therapeutic benefits of NSAIDs with any potential cardiovascular hazards when making judgments. Our results add to the continuing conversation as this field of study develops by highlighting the importance of careful risk assessment and customized patient treatment when it comes to NSAID medication.

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