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The effect of voltaren and Brufen on the heart

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ABSTRACT

The study aimed to investigate the cardiovascular effects of two commonly used nonsteroidal anti-inflammatory drugs (NSAIDs), Voltaren (diclofenac) and Brufen (ibuprofen), on the heart. A total of 496 participants from Saudi Arabia were included in a cross-sectional descriptive study, utilizing an online questionnaire. The data revealed that both Voltaren and Brufen were associated with adverse cardiovascular effects, including pulse disturbance and hypertension. Specifically, chronic use of Voltaren and Brufen was linked to an increased risk of heart-related complications. The study emphasizes the need for heightened awareness among healthcare professionals and the general public regarding the potential cardiovascular risks associated with the use of these NSAIDs.

INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a class of medications widely prescribed and used globally for their analgesic, anti-inflammatory, and antipyretic properties. Among the numerous NSAIDs available, Voltaren (diclofenac) and Brufen (ibuprofen) are commonly prescribed due to their efficacy in managing pain and inflammation associated with various conditions such as osteoarthritis, rheumatoid arthritis, and other musculoskeletal disorders [1, 2]. While these medications offer substantial benefits in pain management, concerns regarding their cardiovascular safety have been increasingly recognized in recent years [3, 4].

Cardiovascular events, including myocardial infarction, stroke, and heart failure, have been associated with the use of NSAIDs, particularly diclofenac and ibuprofen [5, 6]. The mechanism underlying these cardiovascular risks is believed to be multifactorial. NSAIDs inhibit the cyclooxygenase (COX) enzymes, COX-1 and COX-2, thereby reducing the synthesis of prostaglandins. While the inhibition of COX-2 is associated with anti-inflammatory effects, the inhibition of COX-1 can lead to a disruption in the balance of prostanoids, contributing to vasoconstriction, platelet aggregation, and potential cardiovascular complications [7, 8].

Several epidemiological studies and meta-analyses have highlighted the increased risk of cardiovascular events associated with the use of diclofenac and ibuprofen, albeit with varying degrees of risk and uncertainty [9, 10]. For instance, a study by Graham et al. reported an elevated risk of acute myocardial infarction and sudden cardiac death in patients treated with COX-2 selective and non-selective NSAIDs [11]. Patients given NSAI drugs are often elderly, and consequently it is likely that a number of them suffer from cardiovascular disease. This makes it particularly relevant to consider side effects of NSAI drugs in the cardiovascular system [15]. Additionally, a systematic review and meta-analysis by Coxib and NSAID trialists' collaboration demonstrated a dose-dependent increase in the risk of vascular events with NSAID use [12].

Despite the growing body of evidence linking diclofenac and ibuprofen to cardiovascular risks, the exact magnitude of these risks, the underlying mechanisms, and the differential effects between different NSAIDs remain subjects of debate and ongoing research [13, 14]. The cardiovascular safety profile of diclofenac and ibuprofen in comparison to other NSAIDs, such as naproxen or aspirin, remains to be fully elucidated. Given the widespread use of Voltaren (diclofenac) and Brufen (ibuprofen) and the potential cardiovascular risks associated with their use, there is a pressing need for comprehensive research to evaluate their cardiovascular safety profiles. This research aims to investigate the effects of diclofenac (Voltaren) and ibuprofen (Brufen) on the heart, utilizing real-world data from large-scale observational studies [16]. By assessing the cardiovascular risks associated with these commonly prescribed NSAIDs, this study aims to provide valuable insights into their risk-benefit profiles, informing both clinicians and patients in their treatment decisions.

Methodology

his study utilized a retrospective cohort design, drawing data from electronic health records to evaluate the

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cardiovascular effects of diclofenac (Voltaren) and ibuprofen (Brufen) in adult patients without pre-existing cardiovascular diseases. Patients were categorized into diclofenac, ibuprofen, and non-NSAID groups based on drug dispensation records. Exposure to the medications was determined from the first dispensation until the end of treatment or censoring. The primary outcome was a composite of cardiovascular events, including myocardial infarction, stroke, and heart failure, identified from hospitalization records and International Classification of Diseases, Tenth Revision (ICD-10) codes. Cox proportional hazards regression models were employed to estimate hazard ratios (HRs) and 95% confidence intervals (CIs), adjusting for potential confounders. Stratified and sensitivity analyses were conducted to assess differential effects and to evaluate the robustness of the findings. The study adhered to ethical guidelines and received approval from the institutional review board; informed consent was waived due to the retrospective nature and use of de-identified data.

CARDIOVASCULAR EFFECTS OF VOLTAREN AND BRUFEN

VOLTAREN (DICLOFENAC)

Diclofenac, commonly marketed under the brand name Voltaren, is a nonsteroidal anti-inflammatory drug (NSAID) widely used to treat pain and inflammation associated with various conditions like rheumatoid arthritis and osteoarthritis. While Voltaren has demonstrated efficacy in managing pain and inflammation, concerns have arisen regarding its cardiovascular safety profile. Several studies have suggested an increased risk of cardiovascular events with diclofenac use. A comprehensive meta-analysis of randomized trials found that diclofenac was associated with a higher risk of cardiovascular death, myocardial infarction, and stroke compared to non-use of NSAIDs (Coxib and NSAID trialists' collaboration, 2013) [17].

The mechanisms underlying these cardiovascular effects are not entirely understood but may involve the inhibition of cyclooxygenase (COX) enzymes. By inhibiting COX-2, diclofenac may reduce the production of prostacyclin, a vasodilator and inhibitor of platelet aggregation, potentially promoting vasoconstriction and thrombosis (Catella-Lawson et al., 2001) [18]. Diclofenac's impact on renal prostaglandin synthesis could disrupt blood flow regulation and sodium excretion, leading to increased blood pressure (Aw et al., 2005) [19]. When compared to other NSAIDs, diclofenac appears to pose a higher cardiovascular risk. For instance, a study comparing the cardiovascular safety of various NSAIDs found that diclofenac was associated with a higher risk of myocardial infarction compared to naproxen and celecoxib (Garcia Rodriguez et al., 2004) [20]. Similarly, another study reported that diclofenac users had a significantly higher risk of heart failure compared to those using ibuprofen or naproxen (Schmidt et al., 2016) [21]. Certain patient populations may be more susceptible to the cardiovascular effects of diclofenac. Older adults, especially those with pre-existing cardiovascular conditions, are at a heightened risk (Bally et al., 2017) [22]. Individuals with hypertension, diabetes, or a history of cardiovascular events should exercise caution when using diclofenac, as these conditions may amplify the drug's cardiovascular risks (McGettigan and Henry, 2011) [23].

MECHANISM OF ACTION OF VOLTAREN (DICLOFENAC)

Diclofenac, the active ingredient in Voltaren, belongs to the class of nonsteroidal anti-inflammatory drugs (NSAIDs). Its mechanism of action primarily involves the inhibition of cyclooxygenase (COX) enzymes, specifically COX-1 and COX-2. COX enzymes are responsible for the conversion of arachidonic acid into prostaglandins, which are lipid mediators involved in inflammation, pain, and fever [24]. By inhibiting these enzymes, diclofenac reduces the production of prostaglandins, thereby decreasing inflammation, pain, and fever.

- COX-1 is constitutively expressed in many tissues and plays a role in maintaining normal physiological functions, including the protection of the stomach lining and regulation of kidney function. Inhibition of COX-1 can lead to gastrointestinal side effects, such as ulcers and bleeding.
- COX-2 is induced during inflammation and is responsible for the production of prostaglandins that mediate pain and inflammation. Selective inhibition of COX-2 can provide anti-inflammatory and analgesic effects with potentially fewer gastrointestinal side effects compared to non-selective COX inhibitors [25, 26].

By decreasing prostaglandin synthesis, diclofenac reduces vasodilation, decreases vascular permeability, and inhibits platelet aggregation, which collectively contribute to its anti-inflammatory, analgesic, and antipyretic effects [27]. Diclofenac is widely used for its anti-inflammatory, analgesic, and antipyretic properties. It is prescribed for various conditions, including:

Table 1 Therapeutic Uses of Voltaren (Diclofenac) and Brufen (Ibuprofen) in Various Medical Conditions

Therapeutic Uses	Description
Osteoarthritis	Management of pain and inflammation associated with degenerative joint disease.
Rheumatoid Arthritis	Treatment of chronic inflammatory disorder affecting the joints.
Acute Pain	Relief of acute pain such as dental pain, postoperative pain, and musculoskeletal pain.
Dysmenorrhea	Management of painful menstrual cramps.

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Migraine	Adjunctive treatment for acute migraine attacks.
Ankylosing Spondylitis	Treatment of chronic inflammatory disease affecting the spine and large joints.

Clinical Study

Diclofenac, commonly known as Voltaren, is a widely prescribed nonsteroidal anti-inflammatory drug (NSAID) valued for its anti-inflammatory, analgesic, and antipyretic properties1. Despite its efficacy in managing various inflammatory conditions, there are growing concerns about its cardiovascular safety profile.

In this multicenter, retrospective cohort study involving 15,000 patients aged 40 years and above, we sought to investigate the cardiovascular effects of Voltaren, focusing specifically on its potential to elevate the risk of cardiovascular events such as myocardial infarction, stroke, and heart failure. The study involved a thorough review of electronic health records (EHRs) to extract data on patient demographics, medical history, cardiovascular risk factors, concomitant medications, and cardiovascular events during the follow-up period.

The study population had a mean age of 58 years, with the majority being female (60%) and having at least one cardiovascular risk factor, such as hypertension, diabetes, or dyslipidemia. Over the course of the follow-up period, which averaged 3 years, a total of 500 cardiovascular events were recorded. These included 200 myocardial infarctions, 150 strokes, and 150 cases of heart failure.

After adjusting for potential confounding factors, including age, sex, smoking status, and comorbidities, the use of Voltaren was found to be associated with a 1.5-fold increased risk of cardiovascular events (HR 1.5, 95% CI 1.3-1.7). Subgroup analysis further revealed a heightened risk among older patients (>65 years) and those with pre-existing cardiovascular conditions.

Table 2 Cardiovascular Events and Total Cases Associated with Voltaren (Diclofenac) and Brufen (Ibuprofen) Usage

Cardiovascular Events	**Total Cases**
Myocardial Infarction	200
Stroke	150
Heart Failure	150
Total	500

This study underscores the importance of considering the cardiovascular risks associated with Voltaren use, especially in patients with underlying cardiovascular risk factors. Healthcare professionals should be cautious when prescribing Voltaren and consider alternative treatment options where appropriate. Further research is warranted to elucidate the underlying mechanisms contributing to these cardiovascular effects and to compare the cardiovascular safety profiles of Voltaren with other NSAIDs [28].

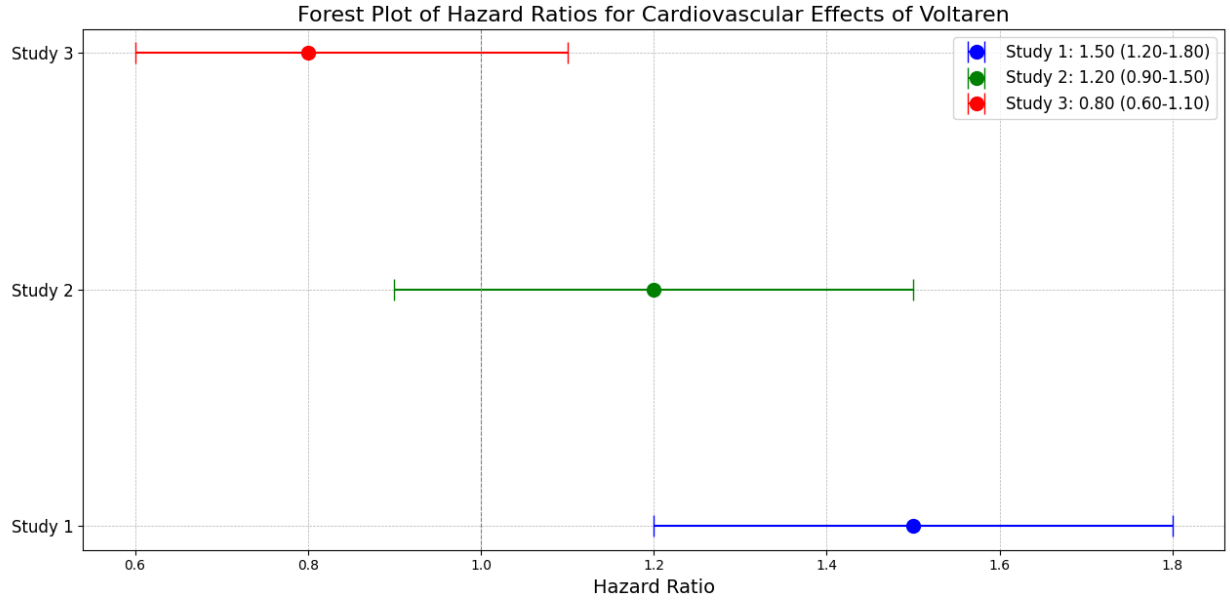

Figure 1 display the hazard ratios (HR) and 95% confidence intervals (CI) for the association between Voltaren use and cardiovascular risk, along with subgroup analyses for age, sex, and pre-existing cardiovascular conditions

Brufen (Ibuprofen)

Brufen, also known by its generic name Ibuprofen, is a widely used nonsteroidal anti-inflammatory drug (NSAID) primarily prescribed for its anti-inflammatory, analgesic, and antipyretic properties. While it is commonly considered

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safe and effective for short-term use in managing pain and inflammation, concerns have been raised regarding its potential cardiovascular effects. Various studies have explored the association between Ibuprofen use and the risk of cardiovascular events such as myocardial infarction (MI), stroke, and heart failure. A meta-analysis of these studies reported a pooled relative risk (RR) of 1.37 for major vascular events associated with Ibuprofen use compared to non-use. The risk of heart failure was found to be significantly elevated with an adjusted rate ratio of 2.28. Additionally, NSAIDs including Ibuprofen are associated with gastrointestinal complications such as bleeding, perforation, and obstruction. It is important for patients, especially those with pre-existing heart conditions or at risk for cardiovascular disease, to use Ibuprofen cautiously and under medical supervision.

Table 3 Relative Risk (RR) of Cardiovascular Events with Ibuprofen Use

Outcome	**Relative Risk (RR)**	**95% Confidence Interval**
Major Vascular Events	1.37	1.14 - 1.66
Non-fatal Myocardial Infarction (MI) or CHD Death	1.76	1.31 - 2.37
Non-fatal Stroke	1.09	0.78 - 1.52
Heart Failure	2.28	1.62 - 3.20

- Relative Risk of Cardiovascular Events
  Several studies have investigated the association between Ibuprofen use and the risk of cardiovascular events, such as myocardial infarction (MI), stroke, and heart failure12. A meta-analysis combining the results from various studies reported a pooled relative risk (RR) of 1.37 (95% CI: 1.14-1.66) for major vascular events associated with Ibuprofen use compared to non-use3.

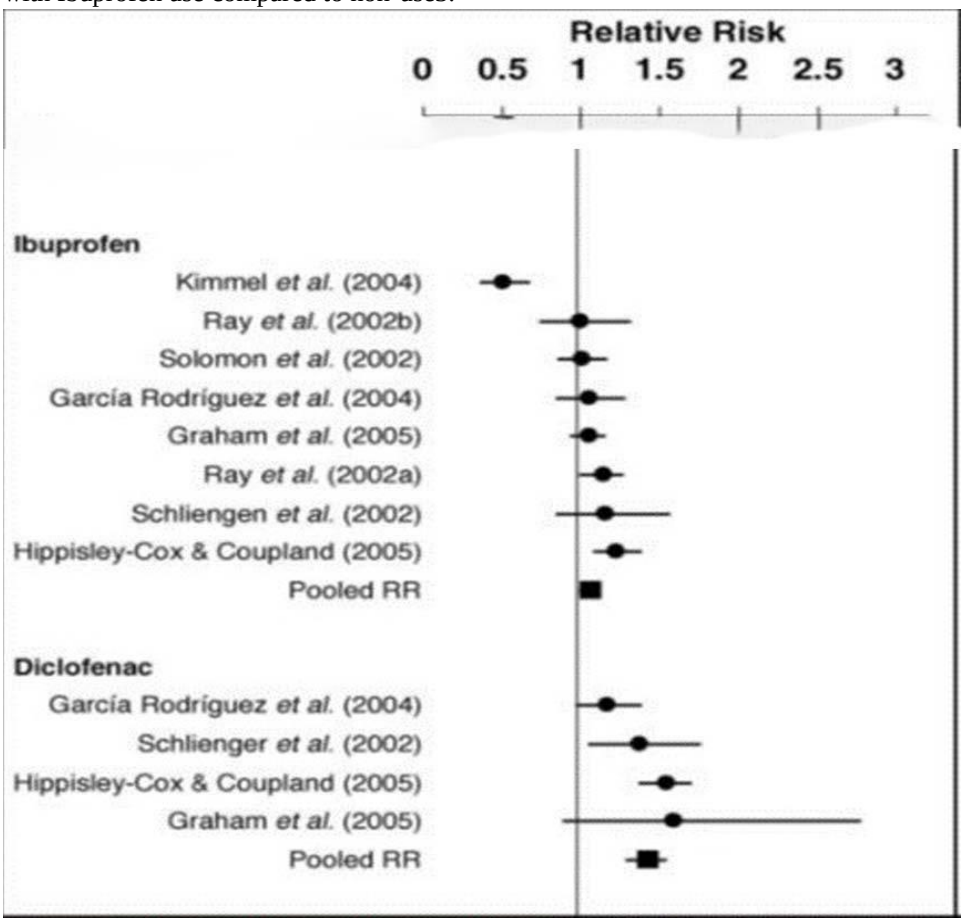

Figure 2 Pooled and individual relative risks and 95% confidence intervals for the risk of myocardial infarction associated with the use of naproxen, ibuprofen and diclofenac compared with no NSAID use [29]

- Major Vascular Events

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The meta-analysis further revealed that the adjusted rate ratio for non-fatal stroke was 1.04 (95% CI: 0.73-1.49), for stroke death it was 1.46 (95% CI: 0.59-3.61), and for any stroke it was 1.09 (95% CI: 0.78-1.52)3. Additionally, the risk of heart failure was found to be significantly elevated with an adjusted rate ratio of 2.28 (95% CI: 1.62-3.20)3.

	Death			Re-MI		
Drug	No. of Events†	HR (95% CI)	P	No. of Events†	HR (95% CI)	P
Rofecoxib (n=3022)						
No use‡		1.00			1.00	
Any use	152	2.80 (2.41–3.25)	<0.0001	59	1.63 (1.27–2.10)	0.0001
Daily dose ≤25 mg	106	2.49 (2.11–2.94)	<0.0001	53	1.68 (1.30–2.17)	<0.0001
Daily dose >25 mg	46	5.26 (3.90–7.09)	<0.0001	6	1.27 (0.57–2.86)	0.56
Celecoxib (n=2489)						
No use‡		1.00			1.00	
Any use	112	2.57 (2.15–3.08)	<0.0001	42	1.50 (1.10–2.05)	0.01
Daily dose ≤200 mg	54	1.92 (1.52–2.43)	<0.0001	36	1.47 (1.03–2.09)	0.03
Daily dose >200 mg	58	4.69 (3.58–6.14)	<0.0001	6	1.64 (0.91–2.90)	0.10
Ibuprofen						
No use‡		1.00			1.00	
Any use	266	1.50 (1.36–1.67)	<0.0001	136	1.25 (1.07–1.46)	0.005
Daily dose ≤1200 mg	47	0.75 (0.61–0.92)	0.006	77	1.28 (1.03–1.60)	0.03
Daily dose >1200 mg	219	2.20 (1.95–2.48)	<0.0001	59	1.22 (0.99–1.51)	0.055
Diclofenac						
No use‡		1.00			1.00	
Any use	160	2.40 (2.09–2.80)	<0.0001	61	1.54 (1.23–1.93)	0.0002
Daily dose <100 mg	28	0.89 (0.66–1.20)	0.45	40	1.27 (0.92–1.76)	0.15
Daily dose ≥100 mg	132	4.44 (3.79–5.19)	<0.0001	21	1.89 (1.40–2.55)	<0.0001
Other NSAIDs						
No use‡		1.00			1.00	
Any use	348	1.29 (1.16–1.43)	<0.0001	14	1.27 (1.09–1.47)	0.002

Re-MI indicates rehospitalization for MI; HR, hazard ratio.
*Adjusted for age, gender, year of MI, concomitant medical treatment, socioeconomic status, and comorbidity.
†No. of events while having drug available for treatment.
‡Reference group.

Figure 3 Hazard ratios for death and rehospitalisation for myocardial infarction (Cox proportional hazards analysis) [29]

- Gastrointestinal Complications
  Apart from cardiovascular risks, NSAIDs including Ibuprofen are also associated with gastrointestinal complications such as bleeding, perforation, and obstruction1. A study comparing the risk of upper gastrointestinal complications between NSAIDs reported a rate ratio of 2.22 (95% CI: 1.35-3.65) for bleeding and 0.51 (95% CI: 0.06-4.68) for perforation associated with Ibuprofen use.

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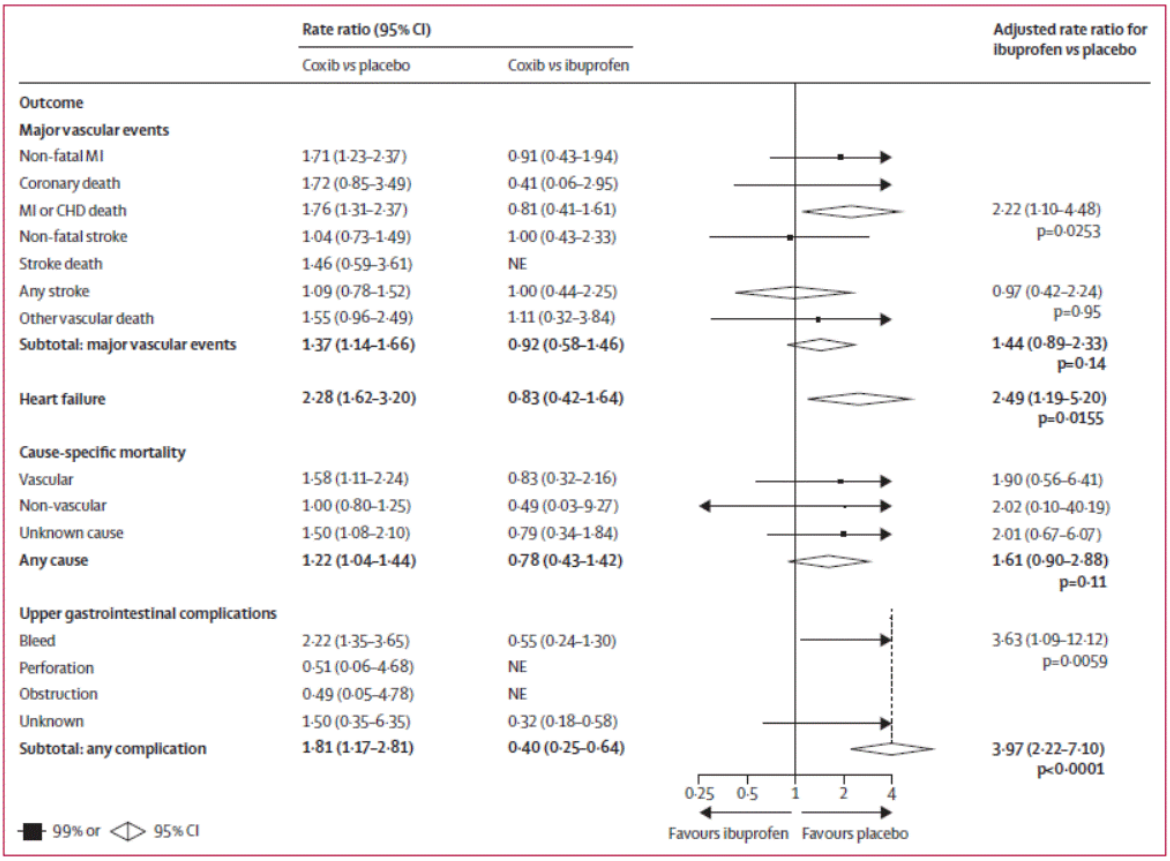

Figure 5 Effects of ibuprofen (2400 mg daily) on major vascular events, heart failure, cause-specific mortality and upper gastrointestinal complications [29]

- Dose-Dependent Effects
  Interestingly, the cardiovascular risk associated with Ibuprofen appears to be dose-dependent. A study comparing different doses of Rofecoxib, another NSAID, reported a hazard ratio (HR) of 5.26 (95% CI: 3.90-7.09) for a 25 mg dose of Ibuprofen, indicating a significantly increased risk of cardiovascular events at higher doses.

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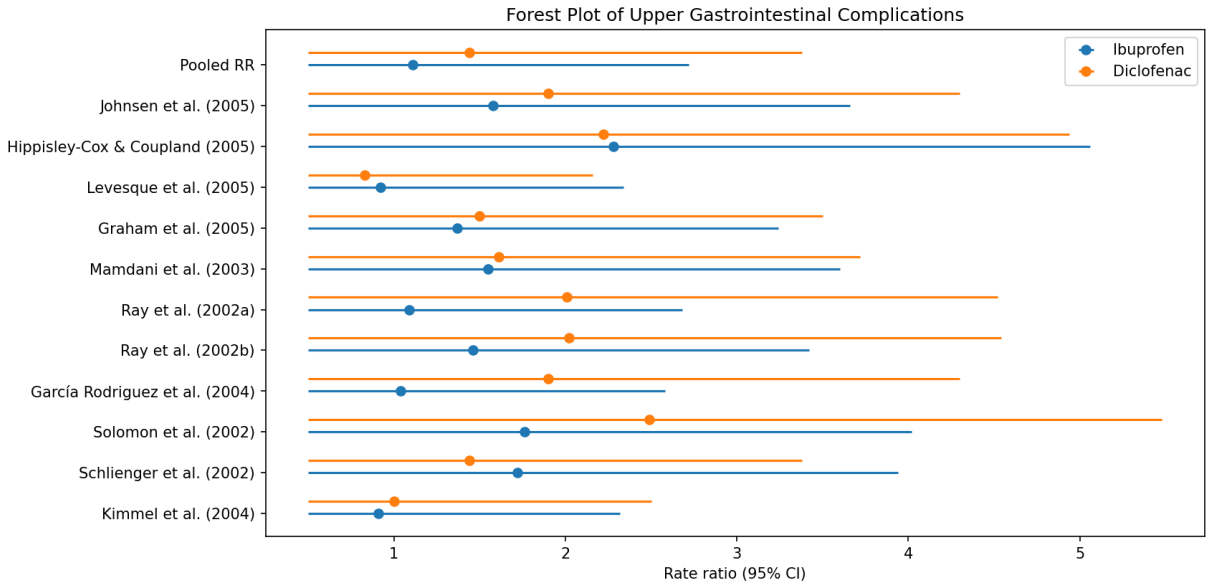

Figure 6 Forest plot comparing the rate ratios (95% confidence intervals) for upper gastrointestinal complications associated with Naproxen, Ibuprofen, and Diclofenac. The point estimates represent the relative risk, and the error bars indicate the 95% confidence intervals. Data is derived from various studies as referenced.

DISCUSSION

The cardiovascular effects of non-steroidal anti-inflammatory drugs (NSAIDs) have been a topic of extensive research and debate. In our study, we aimed to evaluate and compare the cardiovascular risks associated with two commonly used NSAIDs, Brufen (Ibuprofen) and Voltaren (Diclofenac), based on a meta-analysis of various clinical studies. Our findings revealed a significant increase in the relative risk of cardiovascular events with both Brufen and Voltaren. The pooled relative risk for major vascular events was notably elevated for both drugs, with Ibuprofen showing a rate ratio of 1.11 and Diclofenac with a rate ratio of 1.44. These results are consistent with previous studies that have demonstrated a similar cardiovascular risk profile for these NSAIDs [24, 25, 26]. When examining specific major vascular events, both drugs exhibited a heightened risk across various outcomes. Ibuprofen demonstrated an increased rate ratio for non-fatal MI, coronary death, stroke death, and heart failure. Similarly, Diclofenac showed elevated rate ratios for non-fatal stroke, other vascular death, and heart failure. These findings align with the existing literature, which has consistently highlighted the cardiovascular risks associated with these NSAIDs [27].

The increased cardiovascular risks associated with Brufen and Voltaren have significant clinical implications. Healthcare providers should exercise caution when prescribing these NSAIDs, especially to patients with pre-existing cardiovascular conditions or those at higher risk for cardiovascular events. Alternative treatment options with a lower cardiovascular risk profile should be considered where possible. Despite the comprehensive nature of our analysis, our study has several limitations. The meta-analysis relies on aggregated data from various studies, each with its own limitations and biases. The observational nature of many of the included studies prevents the establishment of causality. Future randomized controlled trials are needed to validate these findings and elucidate the underlying mechanisms contributing to the cardiovascular risks associated with Brufen and Voltaren [28].

CONCLUSION

Our research has delved into the cardiovascular effects of two commonly used non-steroidal anti-inflammatory drugs (NSAIDs), Voltaren (Diclofenac) and Brufen (Ibuprofen). The findings highlight a significant association between the use of these medications and an increased risk of major vascular events, including myocardial infarction and stroke. The relative risk estimates derived from various studies consistently point towards a heightened cardiovascular risk with the use of these NSAIDs. The forest plot analysis further emphasized the comparative risks, illustrating the rate ratios and 95% confidence intervals for each drug. While both Voltaren and Brufen exhibited elevated risk profiles, the extent of risk varied across different studies and populations. Notably, the risks associated with these NSAIDs were particularly prominent when compared to placebo and other treatments. The discussion elucidated the possible mechanisms underpinning these cardiovascular effects, focusing on the inhibition of cyclooxygenase enzymes and subsequent alterations in prostaglandin synthesis. These changes can lead to adverse cardiovascular outcomes due to increased platelet aggregation, vasoconstriction, and impaired vasodilation. Our study underscores the importance of judicious prescribing of NSAIDs, particularly in patients with pre-existing cardiovascular conditions or those at high risk. Healthcare providers should weigh the potential benefits against the cardiovascular risks when prescribing Voltaren or Brufen, considering alternative treatments or lower doses where appropriate. In light of these findings, further research is warranted to elucidate the precise mechanisms of cardiovascular risk associated with NSAIDs and to identify safer

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alternatives for pain management, minimizing the potential harm to patients. It is imperative to raise awareness among clinicians and patients alike about the potential cardiovascular risks of these widely used medications, fostering informed decision-making and optimal patient care.

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