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An Analytical Study of NSAIDs Affecting Heart Functions

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Abstract

Local production of vasodilating prostaglandins is necessary to sustain renal perfusion in a number of clinical situations, such as congestive heart failure, cirrhosis, and renal insufficiency. Inhibition of these prostaglandins permits unopposed vasoconstriction to occur when patients with these illnesses are given nonsteroidal anti-inflammatory medicines (NSAIDs), putting them at risk for an acute ischemic insult to the kidney. Acute kidney injury (AKI) and chronic kidney disease are only two of the many nephrological problems that can result from using NSAIDs (CKD). Nonsteroidal anti-inflammatory medicines (NSAIDs) have been shown to increase blood pressure and to antagonize the blood pressure-lowering action of antihypertensive therapy, both of which have the potential to enhance hypertension-related morbidity. Diclofenac was the drug that caused the most noticeable decrease in COX-2 activity, increase in blood pressure, and decrease in heart rate. In a complicated way, non-aspirin, non-steroidal anti-inflammatory medicines (NANSAIDs) can either protect against or contribute to the development of coronary heart disease. The cardiovascular effects of all the medicines studied were unclear, although Naproxen looked the safest. When compared to lumiracoxib, the findings show that ibuprofen may increase the incidence of thrombotic and CHF events in aspirin users with high cardiovascular risk. Before giving a non-steroidal anti-inflammatory medicine, doctors should evaluate the patient for cardiovascular risk.

Key words: Medical, Drugs, Nonsteroidal, Anti-inflammatory Medicines, Diclofenac, heart functions.

1. INTRODUCTION

NSAIDs are commonly used to alleviate pain, reduce inflammation, and lower a high body temperature. Two types of cyclooxygenases (COX) enzymes, COX-1 and COX-2, are responsible for the production of prostaglandins and are the target of their inhibitory effects. Inflammatory, feverish, and painful prostaglandins are produced by both of them. However, only COX-1 generates prostaglandins, which activate platelets and protect the lining of the digestive tract. Therefore, gastrointestinal and intestinal ulcers and increased bleed risk are associated with NSAIDs that inhibit both cyclooxygenase enzymes (COX-1 and COX-2) [1] In this way, indomethacin, diclofenac, naproxen, ketorolac, ketoprofen, and ibuprofen are all non-selective COX inhibitors, while celecoxib, rofecoxib, valdecoxib, and etoricoxib are all selective COX-2 inhibitors [2].

The health benefits of non-selective NSAIDs, a chemically diverse class of compounds used to treat pain and inflammation, are substantial. However, they may cause certain unpleasant side effects in the digestive tract and the cardiovascular system. The therapeutic and harmful effects of these NSAIDs are achieved through the suppression of prostanoid production [3]. Prostanoids, such as prostaglandins (PG), thromboxane A2 (TXA2), and prostacyclin (PC) or prostaglandin I2 (PGI2), are specialised second messengers because they can traverse the cell membrane into the extracellular space and interact with the high-affinity G-protein-coupled receptors on the same or neighbouring cells. They are involved in a wide variety of pathophysiological processes, including the regulation of the inflammatory response, the protection of cells in the digestive tract, blood clotting, and the circulation of blood through the kidneys [4].

In order to reduce pain, fever, and inflammation without negatively impacting the generation of protective PGs by COX-1, selective NSAIDs target and inhibit just this enzyme. But they don't have the same anti-platelet properties as regular NSAIDs. Selective COX-2 inhibitors have a greater impact on PGI2, which is synthesised in the kidney via the COX-2 enzyme, than do non-selective NSAIDs. This results in an imbalance between the effects of PG and PGI2, which enhances the vasoconstriction effects on the cardiovascular system [5].

In situations when there is a drop in either the actual or effective circulatory volume, the vasodilatory PGs function to increase renal blood flow and, by extension, the glomerular filtration rate (GFR). PGI2 increases potassium secretion mostly by promoting renin secretion, while PGE2 also has a function in controlling salt and water reabsorption. That's why preventing cyclooxygenase-2 (COX-2) from working effectively suppresses renin release, while increasing its production results in more PGE2 and PGI2 [6] [7]. Pain or discomfort in the stomach, indigestion, nausea, vomiting, heartburn, disorientation, and diarrhoea are among the most often reported adverse reactions to NSAIDs. Facial puffiness, swelling and oedema of the hands and legs, fainting, trouble breathing, palpitations, and chest tightness are all possible side effects; however, they are quite uncommon [8].

Anti-inflammatory nonsteroidal drugs (NSAIDs) are still widely used and can be purchased without a prescription (OTC). Patients already at high cardiovascular risk may be more vulnerable to their potential for major cardiovascular side effects. Based on research by [9]. Non-selective NSAIDs and selective COX-2 inhibitors can cause varying degrees of salt and water retention; this is thought to be the mechanism behind fluid retention, HTN, and HF. Based on the work of [10].

Some people who use NSAIDs, especially those who already have high blood pressure (HTN), may have an increase in their BP. Non-selective NSAIDs such as indomethacin, diclofenac, naproxen, and piroxicam have been linked to clinically significant changes in blood pressure, but the exact nature of these changes is unclear. As reported by [13], Preliminary research on selective COX-2 inhibitors suggests that etoricoxib is more likely than celecoxib to raise systolic blood pressure (SBP) [11][12]. These NSAID-related BP side effects may be linked to patient characteristics as well as the dose, duration, and kind of medication [14].

Antihypertensive drugs such ACE inhibitors, beta (b) blockers, and diuretics may have their efficacy reduced by the use of non-selective NSAIDs or selective COX-2 inhibitors, thus increasing the HTN-related morbidity. The use of selective COX-2 inhibitors has been linked to an increase in both systolic and diastolic blood pressure (BP) and an increased risk of developing hypertension compared to placebo and non-selective NSAIDs [23][18][19]. Unfortunately, comparing the efficacy of selective COX-2 inhibitors to that of non-selective NSAIDs was not possible due to a lack of observational trials, which may be more reflective of actual clinical practise. The purpose of this research was to evaluate the impact on blood pressure (BP) of the selective COX-2 inhibitor etoricoxib against the non-selective NSAID diclofenac in hypertensive individuals [20][21][22].

2. LITERATURE REVIEW

The following studies have been published about the negative effects of NSAIDs on the function heart and blood vessels:

2.1. Role of NSAIDs in Cardiovascular diseases

Both cyclooxygenase types, COX-1 (whose blockage contributes to an antiplatelet effect) and COX-2, are inhibited by NSAIDs, which is how they work to reduce inflammation (its block has a greater anti-inflammatory, antipyretic and analgesic effect). Although inhibiting COX-2 may lessen gastrointestinal toxicity, it has been proven in several trials to have deleterious effects on heart health. This document's goal is to analyse the side-effects profile of NSAIDs and, more particularly, to explore the cardiovascular repercussions of NSAIDs usage in clinical practise; nevertheless, the mechanisms of the cardiovascular side effects remain contentious. According to a study [36][37].

Over the past several years, numerous clinical trials investigating the efficacy and safety of NSAIDs in CVD have been conducted. Most studies looked at the effect of NSAID usage on CVD in people with a history of CVD. Insufficient research was done on those who had no previous CVD. Nonselective NSAIDs not only cause hypertension in both normotensive and hypertensive persons [33][34], but also counteract the effects of most antihypertensive drugs with the exception of calcium channel blockers. Patients having a previous history of atrial fibrillation, heart failure, myocardial infarction, and other cardiovascular disorders were at a higher risk for developing these illnesses in the future [15][16][17].

2.2. Effects of Diclofenac, Ibuprofen and Naproxen on Heart

The available data on NSAIDs' effects on cardiovascular health were analysed using a network meta-analysis approach. All of the large-scale randomised controlled studies comparing NSAIDs against either other NSAIDs or a placebo were conducted. Myocardial infarction was the major endpoint of interest. Stroke, cardiovascular mortality, and all-cause mortality were secondary results. Patients were randomly assigned to receive either an NSAID (naproxen, ibuprofen, diclofenac, etoricoxib, rofecoxib, or placebo) or no NSAID (placebo). The odds of having a stroke increased by a factor of 3.36 (95% confidence interval: 1.00 to 11.6) among those who used ibuprofen compared to those who took diclofenac (2.86, 1.09 to 8.36). The largest relative risks of mortality from cardiovascular causes were seen with etoricoxib (4.07; 1.23 to 15.7) and diclofenac (3.98; 1.48 to 12.5). It appeared that Naproxen had the fewest side effects [24][25][26].

2.3. NSAIDs causing Myocardial Infarction

The complicated effects of NANSAIDs, or non-aspirin, non-steroidal anti-inflammatory medicines, can either protect against or exacerbate coronary heart disease. Studies comparing the NANSAID rofexocib to naproxen revealed a significant difference in the risk of acute myocardial infarction, which was interpreted as a protective effect of naproxen. To determine the association between naproxen and the development of coronary heart disease, we conducted a prospective research. Acute myocardial infarction or death due to coronary heart disease was the primary outcome of this investigation. Naproxen and similar NANSAIDs should not be used for cardio protection since they do not reduce the risk of developing coronary heart disease. According to a group of researchers [27].

Naproxen, ibuprofen, and piroxicam users were found to have no increased risk of MI [relative rates (RRs) of 0.97, 1.07, and 1.06, respectively] in a recent systematic review of epidemiological studies, while diclofenac and indomethacin users were found to have statistically significant increased risks of MI (RRs of 1.40 and 1.30, respectively [45][46][47][48][49]. Although these results may have some biological support, they may also be explained by differences in how these medications are actually utilised in clinical settings. There have been rumours that some NSAIDs may be diverted to a variety of patients [50][51]. However, while many epidemiological studies have looked at how different NSAIDs affect the risk of MI, the consequences of changes in how people are exposed to those NSAIDs have received less attention. Our study set out to determine if there was a difference in the exposure to and usage of conventional NSAIDs, and if these factors contributed to a difference in the risk of myocardial infarction [49].

Long-term low-dose aspirin therapy lowers the incidence of acute myocardial infarction by roughly 25% and 30%, respectively, in individuals with and without past cardiovascular events, according to randomised clinical studies [38]. Antiplatelet Trialists Collaboration, (2002) found that primary prevention may take years to show a benefit, but the effect for secondary prevention appears to be clinically considerable quickly after commencing treatment. Aspirin's antithrombotic effect is primarily attributable to the full and irreversible inactivation of the cyclooxygenase-1 (COX-1) isoenzyme in platelets, which prevents the production of thromboxane A2, the molecule responsible for triggering platelet aggregation [39].

Individuals with and without preexisting coronary heart disease and those taking and not taking aspirin were compared in a second trial of patients using cyclo-oxygenase-2 and other NSAIDs in primary care between 2000 and 2004. This research used a Nested case-control study design. Myocardial infarction risk appears to be raised with current usage of rofecoxib, diclofenac, and ibuprofen, even after controlling for a number of possible confounders, according to the study's findings [28].

2.4. Role of NSAIDS in vasoconstriction

Myocardial infarction risk may also be affected by using other non-aspirin NSAIDs, albeit this may not be the case in all cases. Traditional NSAIDs (tNSAIDs) may lower cardiovascular risk by lowering inflammation via COX-2 suppression and short-term platelet aggregation via reduced thromboxane A2 production via partial and reversible inactivation of COX-1 [40][39]. On the other hand, NSAIDs might enhance cardiovascular risk by promoting platelet aggregation and vasoconstriction due to their propensity to depress vascular prostacyclin production via COX-2 inhibition [39][41][42]. If the prostacyclin-to-thromboxane A2 haemostatic equilibrium is disturbed, thrombosis may be favored by selective COX-2 inhibitors (Coxibs), especially those with a higher COX-2/COX-1 IC50 binding ratio [43].

2.5. NSAIDs Elevate Blood Pressure

Nonsteroidal anti-inflammatory medicines (NSAIDs) have been the subject of a meta-analysis of randomised trials looking at their impact on blood pressure. Searches of eight databases turned up 38 placebo-controlled randomised studies and 12 randomised trials without placebo (comparing two or more NSAIDs). Blood pressure was elevated by 6.2 mm Hg (CI, 1.1 to 11.4 mm Hg) when combined with -blockers, which was larger than the impact of vasodilators and diuretics combined. Potentially increasing hypertension-related morbidity is the use of nonsteroidal anti-inflammatory medicines, which have been shown to raise blood pressure and counteract the blood pressure-lowering impact of antihypertensive therapy [7].

2.5.1. Etoricoxib and Diclofenac cause Increase in Blood Pressure

Etoricoxib, a selective cyclooxygenase-2 inhibitor, was compared to diclofenac, a nonselective nonsteroidal anti-inflammatory medicine, for its impact on blood pressure in hypertensive individuals in a separate trial. The effects of etoricoxib on the blood pressure of hypertensive individuals were shown to be much greater than those of diclofenac. There was no discernible difference between the two medications with regards to heart rate or renal indicators [35].

Diclofenac is a widely distributed medicine that plays a significant role in the wastewater treatment water cycle. Amphipod embryos were negatively impacted by diclofenac concentrations more than 0.9 g/L, with a higher percentage of embryos showing signs of poor development and ultimately dying as a result. As a result, even at a dosage of 0.1 g/L, diclofenac increased energy expenditure and decreased tolerance to cardiac stress in rats, and at concentrations close to 1 g/L, reproductive problems (increased embryonic mortality) were seen. According to a group of researchers [28][29][30].

A study examined the effects of different antirheumatic dosages of diclofenac, celecoxib, and rofecoxib on cardiovascular parameters (changes in blood pressure and heart rate) in a group of healthy older volunteers. Only at steady state was diclofenac able to elicit nearly full COX-2 inhibition over the whole dosing interval, which correlated with the biggest increase in systolic blood pressure and decrease in heart rate. Diclofenac was the drug that caused the most noticeable decrease in COX-2 activity, increase in blood pressure, and decrease in heart rate [31].

2.6. Ibuprofen causes cardiovascular disturbance

Ibuprofen and diclofenac, both of which belong to a class of medications known as non-steroidal anti-inflammatory drugs (NSAIDs), are widely given across the world and may represent a threat to aquatic life if they make their way into water systems. This study's findings provide new information to our knowledge of the environmental dangers posed by NSAIDs by revealing unanticipated changes in cardiovascular function in fish exposed to these drugs at ambient or somewhat higher than surface water concentrations [32].

In many nations, people turn to ibuprofen when they need to reduce pain, inflammation, or fever. With respect to its anti-inflammatory, analgesic, and antipyretic properties, as well as its potential side effects, the available evidence regarding ibuprofen's mechanisms of action is discussed. Various studies have found an increased risk of cardiovascular (CV) events; however, this is still less than the hazards associated with some coxibs and diclofenac. Patients at risk for CV disorders who use aspirin for prevention of these problems should exercise caution while taking ibuprofen because of the chance that it may interfere with the anti-platelet actions of aspirin, but this impact is likely to be of low grade or importance. The primary findings from this study of the safety and efficacy of ibuprofen for paediatric usage are that it is a useful therapy for both acute pain and fever. As an antipyretic, it is likely more effective than paracetamol [36].

3. CONCLUSION

The usage of nonsteroidal anti-inflammatory medicines (NSAIDs), which are routinely prescribed for the treatment of pain and inflammation, has been linked to an increased risk of cardiovascular events such heart attacks and strokes. People who are already at a higher risk are those who are It is possible to draw the conclusion that over-the-counter pain relievers and anti-inflammatory medications, often known as nonsteroidal anti-inflammatory drugs or NSAIDs, have been associated with an elevated risk of cardiovascular disease and stroke. People who do not already have cardiovascular disease, in addition to those who do, are at an elevated risk. Those who already have preexisting heart issues, on the other hand, are at a greater risk. Nonsteroidal anti-inflammatory medicines, sometimes known as NSAIDs, are readily available without the need for a prescription from a medical professional. In addition, there are several NSAIDs that require a prescription from a medical professional. Celecoxib, ibuprofen, naproxen sodium, and diclofenac

sodium are all examples of nonsteroidal anti-inflammatory medicines. Ibuprofen is sold under the brand names Advil and Motrin IB, and naproxen sodium is sold under the brand names Aleve and Anaprox DS (Celebrex).

The multifaceted effects of NANSAIDs, often known as non-aspirin, non-steroidal anti-inflammatory medications, can either reduce the risk of coronary heart disease or make the condition worse. When certain people use NSAIDs, they could have an increase in their blood pressure (BP), particularly those who already have hypertension and are therefore regarded to be at the greatest risk for such a negative impact. It would appear that indomethacin, diclofenac, naproxen, and piroxicam, which are all examples of non-selective NSAIDs, each have their own unique impact on blood pressure. It is best to use a nonsteroidal anti-inflammatory medication for the shortest length of time necessary and at the lowest effective dose possible. Because of this, there is a decreased likelihood of having a heart attack or a stroke. The vast majority of people are able to take nonsteroidal anti-inflammatory drugs (NSAIDs) on an infrequent basis without putting their health in danger. However, bear in mind that even in the first few weeks of frequent NSAID use, severe side effects might emerge. This is something that should be kept in mind. The longer it takes, the greater the likelihood that something unfavorable will take place.

REFERENCES

1. Jackson, L. M., & Hawkey, C. J. (2000). COX-2 selective nonsteroidal anti-inflammatory drugs: do they really offer any advantages?. *Drugs*, *59*, 1207-1216.
2. COX, F. (2). selective (includes Bextra, Celebrex, and Vioxx) and non-selective non-steroidal anti-inflammatory drugs (NSAIDs).
3. Funk, C. D. (2001). Prostaglandins and leukotrienes: advances in eicosanoid biology. *science*, *294*(5548), 1871-1875.
4. Moore, R. A., Derry, S., & McQuay, H. J. (2007). Cyclo-oxygenase-2 selective inhibitors and nonsteroidal anti-inflammatory drugs: balancing gastrointestinal and cardiovascular risk. *BMC Musculoskeletal Disorders*, *8*, 1-11.
5. Meek, I. L., Van de Laar, M. A., & Vonkeman, H. E. (2010). Non-steroidal anti-inflammatory drugs: an overview of cardiovascular risks. *Pharmaceuticals*, *3*(7), 2146-2162.
6. Harris Jr, R. C. (2002). Cyclooxygenase-2 inhibition and renal physiology. *The American journal of cardiology*, *89*(6), 10-17.
7. Johnson, A. G., Nguyen, T. V., & Day, R. O. (1994). Do nonsteroidal anti-inflammatory drugs affect blood pressure? A meta-analysis. *Annals of internal medicine*, *121*(4), 289-300.
8. Abramson, S. B. (1992). Treatment of gout and crystal arthropathies and uses and mechanisms of action of nonsteroidal anti-inflammatory drugs. *Current opinion in rheumatology*, *4*(3), 295-300.
9. Gordon, D. B. (2003). Nonopioid and adjuvant analgesics in chronic pain management: strategies for effective use. *Nursing Clinics*, *38*(3), 447-464.
10. Crofford, L. J. (2013). Use of NSAIDs in treating patients with arthritis. *Arthritis research & therapy*, *15*, 1-10.
11. Aneja, A., & Farkouh, M. E. (2008). Adverse cardiovascular effects of NSAIDs: driven by blood pressure, or edema?. *Therapeutic Advances in Cardiovascular Disease*, *2*(1), 53-66.
12. Walker, C. (2018). Are all oral COX-2 selective inhibitors the same? A consideration of celecoxib, etoricoxib, and diclofenac. *International journal of rheumatology*, *2018*.
13. Armstrong, E. P., & Malone, D. C. (2003). The impact of nonsteroidal anti-inflammatory drugs on blood pressure, with an emphasis on newer agents. *Clinical therapeutics*, *25*(1), 1-18.
14. Athirakul, K., Kim, H. S., Audoly, L. P., Smithies, O., & Coffman, T. M. (2001). Deficiency of COX-1 causes natriuresis and enhanced sensitivity to ACE inhibition. *Kidney international*, *60*(6), 2324-2329.
15. Fogari, R., Zoppi, A., Carretta, R., Veglio, F., Salvetti, A., & Italian Collaborative Study Group. (2002). Effect of indomethacin on the antihypertensive efficacy of valsartan and lisinopril: a multicentre study. *Journal of hypertension*, *20*(5), 1007-1014.
16. Klassen, D., Goodfriend, T. L., Schuna, A. A., Young, D. Y., & Peterson, C. A. (1993). Assessment of blood pressure during treatment with naproxen or ibuprofen in hypertensive patients treated with hydrochlorothiazide. *The Journal of Clinical Pharmacology*, *33*(10), 971-978.
17. White, W. B., Kent, J., Taylor, A., Verburg, K. M., Lefkowith, J. B., & Whelton, A. (2002). Effects of celecoxib on ambulatory blood pressure in hypertensive patients on ACE inhibitors. *Hypertension*, *39*(4), 929-934.
18. Izhar, M., Alausa, T., Folker, A., Hung, E., & Bakris, G. L. (2004). Effects of COX inhibition on blood pressure and kidney function in ACE inhibitor-treated blacks and hispanics. *Hypertension*, *43*(3), 573-577.

19. Krum, H., Aw, J., & Haas, S. (2004, October). Do selective Cox-Li inhibitors cause more blood pressure elevation than nonselective NSAIDs. In *Circulation* (Vol. 110, No. 17, pp. 434-434).
20. Sowers, J. R., White, W. B., Pitt, B., Whelton, A., Simon, L. S., Winer, N., ... & Safety in Comorbidities Evaluation Trial (CRESCENT) Investigators. (2005). The effects of cyclooxygenase-2 inhibitors and nonsteroidal anti-inflammatory therapy on 24-hour blood pressure in patients with hypertension, osteoarthritis, and type 2 diabetes mellitus. *Archives of Internal Medicine*, *165*(2), 161-168.
21. Krum, H., Swergold, G., Curtis, S. P., Kaur, A., Wang, H., Smugar, S. S., ... & Cannon, C. P. (2009). Factors associated with blood pressure changes in patients receiving diclofenac or etoricoxib: results from the MEDAL study. *Journal of hypertension*, *27*(4), 886-893.
22. Whelton, A., Fort, J. G., Puma, J. A., Normandin, D., Bello, A. E., Verburg, K. M., & Success VI Study Group. (2001). Cyclooxygenase-2–specific inhibitors and cardiorenal function: a randomized, controlled trial of celecoxib and rofecoxib in older hypertensive osteoarthritis patients. *American journal of therapeutics*, *8*(2), 85-95.
23. Aljadhey, H., Tu, W., Hansen, R. A., Blalock, S. J., Brater, D. C., & Murray, M. D. (2012). Comparative effects of non-steroidal anti-inflammatory drugs (NSAIDs) on blood pressure in patients with hypertension. *BMC cardiovascular disorders*, *12*(1), 1-10.
24. Warner, T. D., & Mitchell, J. A. (2008). COX-2 selectivity alone does not define the cardiovascular risks associated with non-steroidal anti-inflammatory drugs. *The Lancet*, *371*(9608), 270-273.
25. White, W. B. (2007). Cardiovascular effects of the cyclooxygenase inhibitors. *Hypertension*, *49*(3), 408-418.
26. Trelle, S., Reichenbach, S., Wandel, S., Hildebrand, P., Tschannen, B., Villiger, P. M., ... & Jüni, P. (2011). Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. *Bmj*, *342*.
27. Ray, W. A., Stein, C. M., Hall, K., Daugherty, J. R., & Griffin, M. R. (2002). Non-steroidal anti-inflammatory drugs and risk of serious coronary heart disease: an observational cohort study. *The Lancet*, *359*(9301), 118-123.
28. Hippisley-Cox, J., & Coupland, C. (2005). Risk of myocardial infarction in patients taking cyclo-oxygenase-2 inhibitors or conventional non-steroidal anti-inflammatory drugs: population based nested case-control analysis. *Bmj*, *330*(7504), 1366.
29. Abramson, A. G., Nguyen, T. V., & Day, R. O. (1994). Do nonsteroidal anti-inflammatory drugs affect blood pressure? A meta-analysis. *Annals of internal medicine*, *121*(4), 289-300.
30. Berezina, N. A., Sharov, A. N., Chernova, E. N., & Malysheva, O. A. (2022). Effects of Diclofenac on the Reproductive Health, Respiratory Rate, Cardiac Activity, and Heat Tolerance of Aquatic Animals. *Environmental Toxicology and Chemistry*, *41*(3), 677-686.
31. Hinz, B., Dormann, H., & Brune, K. (2006). More pronounced inhibition of cyclooxygenase 2, increase in blood pressure, and reduction of heart rate by treatment with diclofenac compared with celecoxib and rofecoxib. *Arthritis & Rheumatism: Official Journal of the American College of Rheumatology*, *54*(1), 282-291.
32. Zhang, K., Yuan, G., Werdich, A. A., & Zhao, Y. (2020). Ibuprofen and diclofenac impair the cardiovascular development of zebrafish (Danio rerio) at low concentrations. *Environmental Pollution*, *258*, 113613.
33. Rorarius, M., Miralles, J., Baer, G. A., & Palomäki, E. (1985). Diclofenac versus indomethacin given as intravenous infusions: their effect on haemodynamics and bleeding time, and side-effects in healthy subjects. *Annals of Clinical Research*, *17*(6), 306-309.
34. Dolanbay, T., Makav, M., Gul, H. F., & Karakurt, E. (2021). The effect of diclofenac sodium intoxication on the cardiovascular system in rats. *The American Journal of Emergency Medicine*, *46*, 560-566.
35. Al-Shehristani, R. M. M., & Aziz, N. D. (2021). The effect of etoricoxib versus diclofenac on blood pressure in hypertensive patients. *JPMA. The Journal of the Pakistan Medical Association*, *71*(12), S18-S23.
36. Rainsford, K. D. (2009). Ibuprofen: pharmacology, efficacy and safety. *Inflammopharmacology*, *17*, 275-342.
37. Marsico, F., Paolillo, S., & Filardi, P. P. (2017). NSAIDs and cardiovascular risk. *Journal of cardiovascular medicine*, *18*, e40-e43.
38. Eidelman , R. , P. Hebert , S. Weisman & C. H. Hennekens : An update on aspirin in the primary prevention of cardiovascular disease. Arch. Int. Med. 2003, 163, 2006– 2010.
39. Patrono , C. , B. Coller , J. Dalen , V. Fuster , M. Gent , L. Harker , J. Hirsh & G. Roth : Platelet-active drugs: the relationships among dose, effectiveness, and side effects. Chest 2004, 126, 234S– 264S.
40. Ross , R. : Atherosclerosis: an inflammatory disease. New Engl. J. Med. 1999, 340, 115– 126.
41. Gurwitz , J. , J. Avorn & R. Bohn : Initiation of antihypertensive treatment during non-steroidal antiinflammatory drug therapy. J. Amer. Med. Ass. 1994, 272, 781– 786.

42. Johnson , A. : NSAIDs and increased blood pressure. What is the clinical significance. Drug Safety 1997, 17, 277– 289.
43. Fitzgerald , G. & C. Patrono : The coxibs, selective inhibitors of cyclooxygenase-2. New Engl. J. Med. 2001, 345, 433– 442.
44. Bombardier , C. , L. Laine , A. Reicin , D. Shapiro , R. Burgos-Vargas , B. Davis , R. Day , M. Ferraz , C. Hawkey , M. Hochberg , T. Kvien , T. Schnitzer & VIGOR Study Group: Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. VIGOR Study Group. New Engl. J. Med. 2000, 343, 1520– 1528.
45. García Rodríguez , L. A. , C. Varas-Lorenzo & C. Patrono : Differential effects of aspirin and non-aspirin nonsteroidal antiinflammatory drugs in the primary prevention of myocardial infarction in postmenopausal women. Epidemiology 2000, 11, 383– 387.
46. Curtis , S. P. , S. Mukhopadhyay , D. Ramey & A. Reicin : Etoricoxib cardiovascular safety summary. Circulation 2003, 108, S1758.
47. Farkouh , M. E. , H. Kirhner , R. A. Harrington , S. Ruland , F. W. Verheugt , T. J. Schnitzer , G. R. Burmester , E. Mysler , M. C. Hochberg , M. Doherty , E. Ehrsam , X. Gitton , G. Krammer , B. Mellein , A. Gimona , P. Matchaba , C. Hawkey & J. J. Chesebro : Comparison of lumiracoxib with naproxen and ibuprofen in the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), cardiovascular outcomes: randomised controlled trial. Lancet 2004, 364, 675– 684.
48. Ott , E. , N. Nussmeier , P. Duke , R. Feneck , R. Alston , M. Snabes , R. Hubbard , P. Hsu , L. Saidman , D. Mangano & Multicenter Study of Perioperative Ischemia (McSPI) Research Group; Ischemia Research and Education Foundation (IREF) Investigators: Efficacy and safety of the cyclooxygenase 2 inhibitors parecoxib and valdecoxib in patients undergoing coronary artery bypass surgery. J. Thorac. Cardiovasc. Surg. 2003, 125, 1481– 1492.
49. McGettigan P, Henry D. Cardiovascular risk and inhibition of cyclooxygenase: a systematic review of the observational studies of selective and nonselective inhibitors of cyclooxygenase 2. *JAMA* 2006; **296**: 1633– 44.
50. MacDonald TM, Morant SV, Goldstein JL, Burke TA, Pettitt D. Channelling bias and the incidence of gastrointestinal haemorrhage in users of meloxicam, coxibs, and older, non-specific non-steroidal anti-inflammatory drugs. *Gut* 2003; **52**: 1265– 70.
51. Leufkens HG, Ameling CB, Hekster YA, Bakker A. Utilization patterns of non-steroidal anti-inflammatory drugs in an open Dutch population. *Pharm Weekbl Sci* 1990; **12**: 97– 103.