A COMPREHENSIVE REVIEW ON NSAIDS AND ITS THERAPEUTIC VALUE

[1]Vineet Kumar [2]Dr. Amandeep Singh, [3]Neelam Painuly, Kamal[4]

[1,4]Research Scholar, Department of Pharmacology, Dev Bhoomi Institute of Pharmacy and research, dehradun.

[2]Professor, Department of Pharmacology, School of Pharmacy and Research, Dev Bhoomi Uttarakhand University, dehradun.

[3]Assistant Professor, Department of Pharmacology, School of Pharmacy and Research, Dev Bhoomi Uttarakhand University, dehradun.

Corresponding Author
VINEET KUMAR M.Pharm (Pharmacology)
Department of Pharmacology, Dev Bhoomi Institute of Pharmacy and research,dehradun
Vineet20mpharco0008@dbit.ac.in
vineetthakur1999@gmail.com

Abstract

NSAIDs, often known as non-steroidal anti-inflammatory drugs, are an example of a prevalent category of painkillers. Despite their extensive usage as painkillers and anti-inflammatory medications, nonsteroidal anti-inflammatory drugs, or NSAIDs, have a large list of adverse effects, some of which include bleeding in the gastrointestinal tract, difficulties with the cardiovascular system, and nephrotoxicity caused by NSAIDs. As a society, we are getting older, and it is more important than ever to have a comprehensive understanding of this class of pharmaceuticals. Because of this, our group investigated the pharmacokinetics and dynamics of NSAIDs, as well as the most recent recommendations for their application, potential adverse effects, and interactions with other medications that are typically provided to older patients.

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Introduction

There are a lot of different words to use to express the sensation of pain, and everyone feels it in a different way. Analgesia should not be confused with nociception, which refers to the transmission of painful sensations to the brain as well as the several processes that are responsible for this transmission. Analgesia is a distinct phenomenon. Therefore, pain is defined as the experience of discomfort, regardless of whether it is generated by the nociceptors, the nerves themselves, or some combination of the two (neuropathic pain) (mixed pain). The term "pain" refers to "an unpleasant sensory and emotional experience connected with actual and potential tissue damage, or articulated in terms of such injury" when referring to an individual's sensation of pain. The analgesic, anti-inflammatory, and fever-

reducing effects of non-steroidal anti-inflammatory drugs (NSAIDs) have contributed to the widespread use of these medications. NSAIDs make up between 5 and 10 percent of the total pharmaceuticals that are prescribed worldwide each year, making them one of the types of treatments that are prescribed the most frequently. Elderly people frequently take non-steroidal anti-inflammatory drugs (NSAIDs), and the fact that they are involved in such a wide range of medications, both prescription and over-the-counter, puts them at risk for polypharmacy, drug-drug interactions, and ultimately, drug-related problems and even mortality. Because long-term use of NSAIDs has been related to serious and sometimes fatal gastrointestinal side effects such ulcers and bleeding, co-prescribing gastro-protective medications is necessary for preventing these risks. There is a connection between nonsteroidal anti-inflammatory drugs (NSAIDs) and 29% of fatal peptic ulcer complications in the elderly. Gastro-protective medications were underutilised in conjunction with NSAIDs, and the other substantial side effects identified with NSAIDs contribute to the anxiety that this situation exists.

Patients over the age of 65 who take more than one medicine per prescription are at an increased risk for experiencing serious adverse reactions to their medication, according to a number of studies. Because doctors do not have a complete understanding of how drugs interact with one another, the relevant risk that is posed by the administration of many medications at the same time is frequently underestimated.

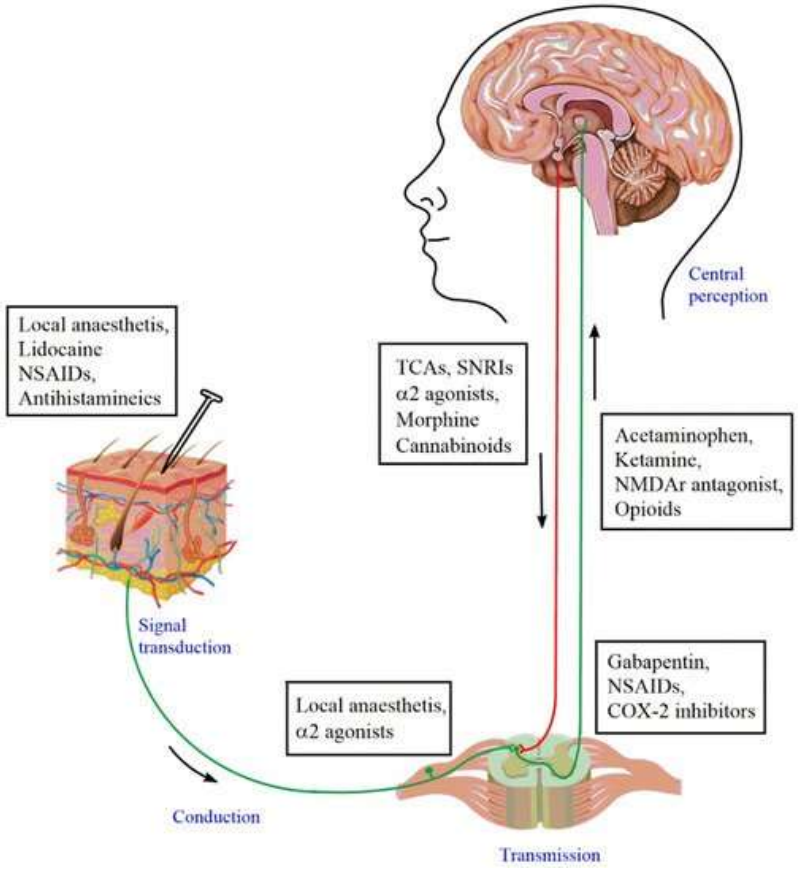

Fig: 1 Pain pathway and pharmacological interventions. From tissue trauma to central sensitization, different analgesics are known to act at various points of pain transmission. At the site of injury, local anaesthetics, antihistamines, and anti-inflammatory agents can be used for direct pain relief. Opioids and non-opioid drugs including morphine, cannabinoids, COX-2 inhibitors, α2 agonists, gabapentin, acetaminophen, and tricyclic anti-depressants (TCAs) act both peripherally as well as centrally, hence attenuating the transmission of pain signaling.

It is possible to separate the steps of a painful experience into the following categories: transduction, transmission, and modulation (fig: 1). Nociceptors are activated in response to noxious stimuli at specific tissue regions, which in turn sets off the transmission process. The action potentials that are created are sent, via a faster A-delta transmission and a slower C fibre transmission, to the dorsal horn of the spinal cord, then to the thalamus, and lastly to the cerebral cortex. When the inhibitory pathways in the brain and brainstem are stimulated, there is a possibility that nociceptive signals will be altered, which will then result in altered afferent signals that will eventually reach the brain. The key regions of the brain that are responsible for the perception of nociceptive impulses are the somatosensory, prefrontal, insular, and cingulate cortices.

It is possible that polypharmacy is unavoidable in this population; nonetheless, medical professionals are required to adhere to the most recent standards and always maintain an up-to-date understanding of the potential interactions, safety signals, and risk mitigation strategies.

In terms of clinical practise, there is a substantial gap between what is conceptually known and what can really be carried out in the real world. According to the authors' understanding, an examination into the use of NSAIDs by older people in Eritrea has not yet been finished. Recent studies have shown that due to a shortage of physicians, common practises such as self-medication and the distribution of pharmaceuticals that are not available over-the-counter without a prescription are common.

Pharmacokinetics & Pharmacodynamics of NSAIDS

The nonsteroidal anti-inflammatory drug (NSAIDS) pharmacokinetics (PK) and pharmacodynamics (PD) (NSAIDs). It is not intended to be comprehensive, as it does not cover a number of insignificant species as well as numerous essential qualities of NSAID PD. Integration of PK-PD data and modelling of PK-PD relationships are the primary foci of this review, which also aims to summarise important aspects of NSAID pharmacokinetics and pharmacodynamics (the subject of the next review in this issue). In general, the pharmacokinetics of NSAIDs are distinguished by a number of characteristics, including good oral bioavailability, high plasma protein binding, low distribution volumes, limited excretion of administered dose as parent drug in urine, marked inter-species differences in clearance and elimination half-life, and easy penetration into and slow c-reactive protein in most species. These characteristics can be broken down as follows: good oral bioavailability; high plasma protein binding; low distribution volumes; limited excretion of Analgesics, such as nonsteroidal anti-inflammatory drugs (NSAIDs), have effects on the body that are both local and systemic. It is generally agreed that the major mechanism of action of NSAIDs at the molecular level is the inhibition of the arachidonic acid cascade enzyme known as COX, which is responsible for the production of inflammatory mediators belonging to the prostaglandin group. On the other hand, nonsteroidal anti-inflammatory drugs (NSAIDs) have a diverse spectrum of molecular actions. There are two distinct variants of the COX enzyme, and one of these has been designated an isoform. It is believed that the majority of the negative effects of NSAIDs are caused by the inhibition of COX-1, but it is impossible to say for certain whether or not COX-1 also plays a little part in the therapeutic effects (such as the analgesic and anti-inflammatory characteristics). The capacity of NSAIDs to suppress COX-2 enzymes is likely responsible for the bulk of the positive effects that these medications have, if not all of them. As a result, there has been a significant push in the direction of discovering and developing COX-2 selective inhibitors. Quantitative data on the three important PD parameters (efficacy, potency, and sensitivity) for the inhibition of COX isoforms by NSAIDS can be obtained through an in vitro investigation of whole blood COX-1:COX-2 inhibition ratios. There are species differences in NSAID-induced COX inhibition, according to the limited published data. This is true for both the potency and the potency ratios. NSAIDs derived from 2-arylpropionate are permitted for use as racemic mixtures despite the fact that they are available in both the R-(-) and S-(+) enantiomeric

forms. In the case of certain drugs, there are substantial variances between species in the pharmacokinetic and pharmacodynamic properties of individual pharmaceuticals in a given species.

Current Guidelines for using a NSAIDS

PCPs generally lack knowledge of the adverse effects that NSAIDs can have on the cardiovascular system, the gastrointestinal tract, and the kidneys. Because of this, doctors who prescribe NSAIDs might not notice certain risk factors in their patients. On the other hand, a suboptimal dose of an NSAID may be prescribed for pain treatment because of an overestimation of the risk associated with NSAIDs. In addition, patients who take nonselective NSAIDs purchased over the counter are typically unaware of the risks associated with long-term use of these medications. In addition to that, it would be beneficial to have a fresh set of guidelines for clinical practise that are derived from the findings of more recent research. There are currently no additional COX-2 inhibitors available for purchase outside celecoxib, etoricoxib, and paracifloxacin. These three are the only ones. Oral preparations of celecoxib, etoricoxib, and parecoxib can be administered, but parecoxib is the prodrug of valdecoxib that is administered intravenously. Rofecoxib, valdecoxib, and lumiracoxib have all been removed from the market as a result of safety concerns related to the cardiovascular system as well as serious dermatological reactions. There is currently insufficient evidence to either support or reject the use of NSAIDs in the treatment of COVID-19 patients. This is despite the fact that corticosteroids may be beneficial if given early on in the acute phase of the illness. It is essential, however, to stress that this is not solely an issue with COVID-19. Because 'glucocorticoid-mediated stimulation of the hypothalamic-pituitary-adrenal axis may also drive lymphocytopenia, or it may promote exaggerated pro-inflammatory responses that eventually cause a worsening of the pathogenic condition,' the World Health Organization (WHO) does not currently recommend corticosteroids in other viral diseases, such as Dengue. Even if non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids are able to be utilised in the treatment of COVID-19, extreme caution should be exercised until evidence that is unique to this viral strain is developed. The field of medicine is currently through a period of extraordinary change. Patients diagnosed with cancer should heed the same counsel and refrain from making any changes to their prescribed medication schedule unless specifically instructed to do so by their treating physician.

High dose of NSAIDS Causes Adverse Effects

Kidney and NSAIDS

Selective inhibitors of the second cyclooxygenase isoform have been produced as a result of the discovery of the first cyclooxygenase isoform, which may have the effect of reducing the negative side effects of COX-1 inhibitors. It was believed up until fairly recently that the COX-2 isoform was only activated in regions of inflammation, hence avoiding the harmful implications of COX-1 inhibition. However, current research has disproved this theory.

Whether or not an NSAID is selective for one of the two COX isoforms that reside in the kidneys can have a significant impact on the renal function and cause it to be altered in a variety of ways. Inhibition of COX-1, which promotes natriuresis, has the potential to lower blood pressure, but blockage of COX-2 has the potential to cause sodium and water retention, which has the potential to elevate blood pressure. Prostacyclin and prostaglandin E2 are two of the most well-known prostaglandins (PGs) that have an effect on kidney function (PGI2). When the circulation is reduced, the PGs cause a rise in both the renal blood flow and the glomerular filtration rate. In addition to this, potassium ions will be released from the tubules as a consequence of this process. When there is not enough blood flowing through the kidneys, one essential compensatory mechanism is the synthesis of PG by the kidneys. In addition to stimulating the renin–angiotensin system and increasing the amount of renin that is secreted, PGI2 and maybe PGE2 also increase the amount of potassium that is secreted. This causes an increase in the amount of aldosterone that is secreted. PGE2, which acts as a counter-regulatory factor in conditions in which there is an excessive amount of sodium reabsorption, is one of the factors that

controls the reabsorption of sodium as well as water. As a result of PGE2's inhibition of the Na+K+2Cl cotransporter type 2, the amount of sodium that can be reabsorb on the thick ascending limb of the Henle loop is reduced (NKCC2). Altering the control of NKCC2 in the thick ascending limb of the Henle loop and aquaporin2 in the collection tube are two ways that an increase in urine concentrating capacity can be achieved. These medications have the potential to be helpful in treating a variety of illnesses, including Bartter's disease and nephrogenic diabetic insipidus. Because of the effects of the arginine vasopressin, the distal nephron as well as the renal interstitial space get flooded with kinins, which results in an increase in the synthesis of PGE2 in the kidney collecting ducts. The renal medulla is the major area of the kidneys responsible for the reabsorption of salt, chloride, and water. The reduction of COX-2, which has been associated to the retention of salt and water, may result in a decrease in the amount of medullary PGE2 that is present. It has been demonstrated that angiotensin II and noradrenaline both work to decrease renal blood flow; hence, it was hypothesised that COX-2 produced PGs may be employed to maintain renal blood flow even in the absence of angiotensin II or noradrenaline. Inhibiting COX-1 decreased levels of prostaglandin G (PG) in all three regions of the kidney, whereas inhibiting COX-2 decreased levels of PG only in the renal medulla. These findings are based on the findings of a study that was carried out on mice. It was previously believed that NSAIDs had a detrimental effect on renal function, as demonstrated in Figure 2.

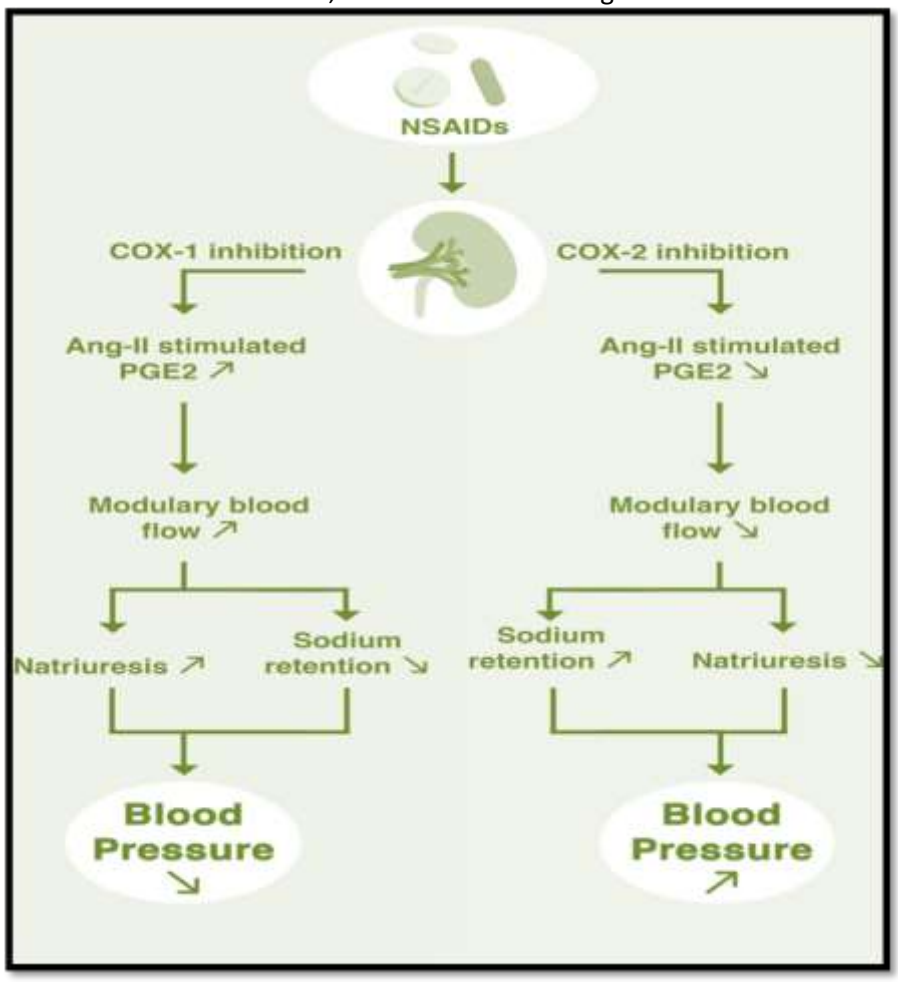

Fig: 2 COX-1 and COX-2 inhibition has renal consequences. Ang II, angiotensin II; NSAID, nonsteroidal anti-inflammatory medications; PGE2, prostaglandin E2

GI and NSAIDS

The annual cost of NSAIDs around the globe is in the billions of dollars. The usage of NSAIDs is extremely common. Even while side effects, particularly in the gastrointestinal (GI) tract, are generally uncommon, the widespread use of these drugs has resulted in a significant strain being placed on the health care systems of countries all over the world. Dyspepsia, erosive gastric lesions and peptic ulcers, perforation, and obstruction of the esophageal sphincter are some of the conditions that fall into this category. Dyspepsia can be diagnosed in some cases without the need for an endoscopy. The reduction of gastric prostaglandins as a result of COX-1 inhibition and the irritation of the gastroduodenum by topical agents are two of the most commonly postulated mechanisms for gastroduodenal injury. There are a number of factors that have been linked to an increased likelihood of developing peptic ulcers or ulcer complications, including advanced age, a history of ulcers, and concomitant use of steroids or anticoagulants. The co-prescribing of gastroprotective medications with safer nonsteroidal anti-inflammatory drugs (NSAIDs), such as COX-2 inhibitors, is one way for reducing adverse gastrointestinal (GI) events. Misoprostol and proton pump inhibitors are effective treatments for uremic ulcers brought on by nonsteroidal anti-inflammatory drugs (NSAIDs). The importance of eliminating Helicobacter pylori in the treatment and prevention of ulcers caused by nonsteroidal anti-inflammatory drugs (NSAIDs) is a contentious topic of discussion. The choice of nonsteroidal anti-inflammatory drugs (NSAIDs) and gastroprotective drugs ought to be guided by risk-benefit and cost-effectiveness evaluations.

CHF and NSAIDS

If prostanoid synthesis is blocked, it is possible that the kidney's glomerular filtration, as well as its salt and water excretion, will be diminished. As a consequence of this, using NSAIDs is associated with an increased risk of hypervolemia and a worsening of heart failure. If a patient already has congestive heart failure (CHF), especially if they are taking diuretics to control their condition, then their risk is significantly increased.

According to the findings of a study carried out by Heerink et al., the administration of NSAIDs to participants who were also taking diuretics resulted in an increased risk of heart failure hospitalisation of 1.8 (95 percent CI= 1.4-2.4). The fact that individual NSAIDs did not differ considerably from one another lends credence to the concept of a class effect. The first few days of treatment had a significant risk of heart failure worsening, but this risk gradually lessened over the course of a month.

The possibility of requiring hospitalisation due to heart failure was evaluated in patients using NSAIDs. NSAID users were observed to have a relative risk that was 2.1 percent higher than non-users when the two groups were compared. When cardiovascular disease was already present, the relative risk (RR) of dying was dramatically increased (10.5). According to the authors of the study, the use of NSAIDs may be connected to as much as 19 percent of newly diagnosed cases of congestive heart failure. As a result of the medical community's perception that the risk of CHF exacerbation induced by NSAIDs appears higher than the risk of other CV adverse effects, people who have CHF are less likely to be prescribed an NSAID than those who have other types of CV disease, as shown by recent statistics. This is in contrast to people who have other types of CV disease.

Blood Pressure & NSAIDS

ACE inhibitors, also known as angiotensin-converting enzyme inhibitors, have been proven to reduce blood pressure in older adults. On the other hand, indomethacin has been demonstrated to have little to no effect on blood pressure in patients who are also taking dihydropyridine calcium blockers (amlodipine or felodipine). In hypertensive patients who are

currently being treated, clinical observation and reports of adverse medication reactions show that COX-2 inhibitors may cause an increase in blood pressure. It has been hypothesised that rofecoxib and celecoxil may produce distinct physiological responses in the body. It would appear that NSAIDs have a variety of effects on blood pressure; however, this may be because to the varying degrees of COX inhibition provided by each medication. After the discovery of indomethacin, researchers began working on medications with the intention of producing fewer side effects on the gastrointestinal mucosa and fewer instances of blood loss. In order to accomplish this goal, it is likely that lower doses were necessary, and the anti-inflammatory impact may not have been as complete as it was when using indomethacin. This is without a doubt the situation. As a consequence, this led to a greater analgesic impact, but it also led to a bigger influence on renal function with the introduction of COX2 inhibitors, which were less likely to cause stomach bleeding. Salt retention can lead to an increase in blood pressure, which can be dangerous. Although we hypothesise that the majority of nonsteroidal anti-inflammatory medicines, also known as NSAIDs, can cause an increase in blood pressure in those who are already predisposed to having hypertension, this is not the case with aspirin, which is used as a prophylactic precaution.

Although nonsteroidal anti-inflammatory drugs (NSAIDs) have been associated to a rise in blood pressure, the exact mechanism that causes this rise is yet unknown. We think that fluctuations in renal blood flow and the glomerular filtration rate, which are responsible for sodium retention, are to blame for this phenomenon. When sodium is retained in the body or when a person consumes a lot of salt, high blood pressure is not a symptom that occurs in every individual. Salt can cause severe reactions in some people while having no effect on others at all. It is possible that nonsteroidal anti-inflammatory drugs (NSAIDs) do not cause an increase in blood pressure in salt-sensitive patients. This hypothesis may help to explain why Johnson et almeta-analysis .'s did not find any clinical effects in a number of investigations, particularly in young volunteers. Ibuprofen was shown to raise blood pressure in a group of senior people with normal blood pressure, but it had no effect on a group of younger people, according to research by Mulkerrin and colleagues. The majority of antihypertensive medicines cause sodium retention, which lowers the efficacy of the medication to lower blood pressure. Therefore, the effect of treating hypertension with blockers, ACE inhibitors, and vasodilators, in addition to sodium restriction or diuretics, results in an even higher reduction in blood pressure. Calcium blockers that contain dihydropyridine, on the other hand, have no impact on a person's blood pressure if that person already has their blood pressure under control. However, the addition of a diuretic will cause an increase in blood pressure in the event that a nondihydropyridine is ineffective. We believe that renal function will be affected by all NSAIDs and that salt retention will occur when all medications are taken in the same doses. The response of the patient's blood pressure will be influenced by their sensitivity to salt. If they are susceptible to salt, their blood pressure will begin to rise.

Conclusions

It is absolutely necessary to have knowledge about pharmacological mechanisms of action, current guidelines, and adverse drug reactions, in addition to pleiotropic effects, in order to provide comprehensive treatment for elderly patients. NSAIDs are commonly prescribed to older patients for the treatment of a wide range of conditions. To ensure the most favourable outcomes, these medications ought to be administered for the shortest amount of time that is practically possible, at the lowest effective dose, and with close attention paid to the toxicity of their effects on the gastrointestinal tract, the renal system, and the

cardiovascular system. Particularly susceptible to the potentially harmful effects of nonsteroidal anti-inflammatory medicines are people who have reached their senior years (NSAIDs). According to the findings of many pieces of research, using NSAIDs can help reduce the risk of cancer, improve muscle performance, and lessen the likelihood of having urinary incontinence. Additionally, there is a correlation between the use of NSAIDs and an increased risk of geriatric mental episodes, an increased risk of stroke, and an increased risk of falling in the older population. Therefore, it is necessary that these risks and advantages be carefully balanced in individual patients to guarantee the best possible outcomes, particularly for senior patients. This is particularly important to do when dealing with elderly patients.