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Nonsteroidal Anti-Inflammatory Drugs and Heart Failure

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Abstract

Heart failure constitutes an increasing public health problem because of the growing incidence and prevalence, poor prognosis and high hospital (re)admission rates. Myocardial infarction is the underlying cause in the majority of patients, followed by hypertension, valvular heart disease and idiopathic cardiomyopathy.

Nonsteroidal anti-inflammatory drugs (NSAIDs), which inhibit the enzymes cyclo-oxygenase (COX) 1 and 2, have been associated with the occurrence of symptoms of heart failure in several case reports and quantitative studies, mainly in patients with a history of cardiovascular disease or left ventricular impairment. NSAIDs may impair renal function in patients with a decreased effective circulating volume by inhibiting prostaglandin synthesis. Consequently, water and sodium retention, and decreases in renal blood flow and glomerular filtration rate may occur, affecting the unstable cardiovascular homeostasis in these patients. In patients with pre-existing heart failure, this may lead to cardiac decompensation. Putative renal-sparing NSAIDs, such as COX-2 selective inhibitors have similar effects on renal function as the traditional NSAIDs, and can likewise be expected to increase the risk of heart failure in susceptible patients. NSAIDs are frequently prescribed to elderly patients, who are particularly at risk for the renal adverse effects. If treatment with NSAIDs in high risk patients cannot be avoided, intensive monitoring and patient education is important.

Heart failure constitutes a major public health problem. The prevalence in the general population is estimated to range from 0.3 to 2.0%, and increases considerably with age.[1] It approximately doubles with every additional decade of life.[2] Estimates of the cumulative incidence per year follow a similar pattern and vary from 0.1 to 0.2% in middle aged men and women.[1] In the last two decades, hospital admission rates for heart failure have increased steadily.[3] Readmissions for exacerbating heart failure occur frequently, especially in the elderly. The incidence of heart failure increases over calendar time, which is most likely explained by improved survival after myocardial infarction (MI), and increased longevity in industrialised countries. Prognosis remains poor, with a cumulative 5-year mortality of over 40%.[4] Because of the increasing number of patients with heart failure, and its high

morbidity and mortality, it is important to identify potentially preventable risk factors for the occurrence of heart failure.

Heart failure can result from any structural or functional disorder that impairs the ability of the left ventricle to fill with or eject blood.[5] Diagnosis is complex and relies on clinical judgement based on history, physical examination and imaging procedures, such as echocardiography. Characteristically, patients present with signs of breathlessness or fatigue, either at rest or during exertion, pulmonary crepitations or peripheral oedema.[6] Symptom-free periods are often alternated with periods of exacerbating symptoms. Heart failure develops when compensatory haemodynamic and neurohormonal mechanisms of the injured heart are exhausted or overwhelmed.[7] As coronary heart disease is the underlying cause in the majority of patients, most have evidence of left ventricular systolic dysfunction. However, nearly all patients also exhibit diastolic impairment at rest.[6] This report focuses mainly on heart failure due to systolic dysfunction. The most frequent non-ischaemic causes of heart failure are hypertension, valvular disease and idiopathic dilated cardiomyopathy.[5]

Several drugs have been demonstrated to be able to induce or exacerbate heart failure.[8] In a number of reports, the occurrence of heart failure was attributed to the use of nonsteroidal anti-inflammatory drugs (NSAIDs).[9-13] NSAIDs are used extensively in the general population for rheumatological conditions, especially in elderly patients. Nonrheumatic indications include acute and chronic pain, biliary and ureteric colic, and dysmenorrhoea.[14] In the US, 70 million NSAID prescriptions are dispensed each year.[15] Worldwide these agents account for approximately 2.5% of all prescription dollars, corresponding with $US6.8 billion spent annually.[16] Most patients who use therapeutic dosages for a short period of time tolerate NSAIDs well.[17] However, a considerable subset of individuals develop adverse effects involving the gastrointestinal, renal and cardiovascular systems.

In this report, we discuss recent findings on the association between the use of NSAIDs and the occurrence of heart failure. Consecutively, we focus on current knowledge of the pathophysiology of heart failure, the mechanism of action and renal effects of NSAIDs, potential 'renal-sparing' NSAIDs, cyclo-oxygenase (COX)-selectivity, and quantitative studies on the association between NSAIDs and heart failure.

1. Pathophysiology of Heart Failure

Left ventricular dysfunction begins with some form of injury to the myocardium, for example an acute MI, which results in loss of functioning myocardial cells. In response, haemodynamic and neurohormonal mechanisms are activated to preserve cardiac function.[18] The decreased capacity of the left ventricle to empty during systole increases diastolic wall tension in the non-injured parts of the heart. The left ventricle responds by enhancing its contraction, following the Frank-Starling curve. Additionally, the sympathetic nervous system is activated, resulting in increased force and frequency of contraction. Both compensatory mechanisms also lead to a remarkable increase in internal wall stress during diastole. In response, synthesis of myofibrillar proteins is stimulated, resulting in increased wall thickness and a subsequent reduction of ventricular wall stress and dilatation, which reduces energy expenditure.[7] Moreover, an increase in diastolic wall stress in the atria suppresses the sympathetic nervous system[19] and leads to the release of atrial (A-type) natriuretic peptide. In addition, B-type natriuretic peptide and C-type natriuretic peptide are released, respectively, by the ventricular myocardium in response to elevations of end-diastolic pressure and volume, and by endothelial cells in response to shear stress.[20] The natriuretic peptides improve the loading conditions on the heart through their diuretic, natriuretic and vasodilator properties. In this way, a delicate haemodynamic balance is achieved, which restores cardiac function.[7]

Long-term activation of these mechanisms, however, diminishes their favourable physiological effects and results in progressive deterioration of ventricular function. As cardiac output declines, systemic perfusion is maintained by peripheral

vasoconstriction and sodium retention.[21] Catecholamines, angiotensin II and vasopressin act to increase systemic blood pressure and expand intravascular volume, while prostaglandins and natriuretic peptides limit the pressor, antinatriuretic and antidiuretic effects of these vasoconstrictor systems. Water and salt retention result mainly from direct and indirect effects of the renin-angiotensin system on glomerular and tubular function.

2. Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

2.1 Mechanism of Action

NSAIDs are a structurally diverse group of drugs containing the salicylates, pyrazoles, oxicams, fenamates, arylacetic acids and arylpropionic acids.[22] They exert analgesic, antipyretic, anti-inflammatory and platelet-inhibitory actions. Inhibition of prostaglandin synthesis, through inhibition of COX, is the major mechanism of action.[23] This enzyme metabolises arachidonic acid to prostaglandin (PG) G_2. This is reduced to PGH_2, the precursor of various other prostaglandins, prostacyclins and thromboxanes. COX consists of at least two different isoenzymes. COX-1 is constitutively expressed, and regulates functions such as gastric cytoprotection and vascular homeostasis.[24] COX-2 is predominantly present throughout all stages of the inflammatory response but is also constitutively expressed in parts of the kidney.[16] Most NSAIDs inhibit both COX-1 and COX-2, but in recent years selective COX-2 inhibitors, such as celecoxib and rofecoxib, have been developed.

2.2 Effects on Renal Function

At present, it is believed that the central mechanism by which NSAIDs influence cardiovascular homeostasis follows from their effect on renal function. Potential prostaglandin-mediated renal adverse effects of NSAID therapy are summarised in figure 1. Prostaglandins are known to exert their effects at the location at which they are synthesised and are therefore referred to as autocoids. The major sites of COX in the kidney comprise the arterial tree, including the afferent and efferent arterioles, the glomerulus and the collecting tubule. Furthermore, interstitial cells adjacent to the thick ascending limb of Henle's loop and in the medulla are rich in COX.[25]

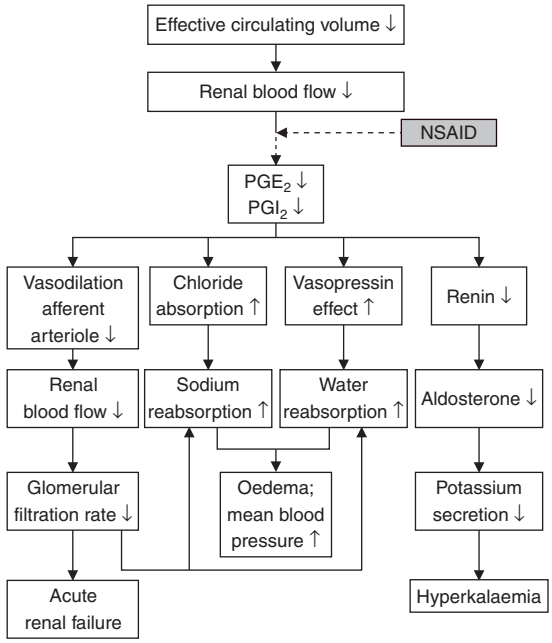

Fig. 1. Prostaglandin-mediated renal adverse effects of NSAIDs with a potential effect on cardiovascular homeostasis. Effects of angiotensin II and natriuretic peptides A, B and C, which are released in response to a decrease and an increase, respectively, in effective circulating volume are not shown in this figure. **PG** = prostaglandin; ↓ indicates decreased; ↑ indicated increased.

Under normal, euvolaemic conditions, prostaglandins do not play a major role in the maintenance of renal and glomerular circulation.[26] However, in settings of decreased effective circulating volume, such as heart failure, hepatic cirrhosis, chronic renal insufficiency and dehydration, prostaglandin production is enhanced to preserve renal perfusion.[27] Whenever renal blood flow is compromised, the kidneys respond by releasing two types of hormones, angiotensin II and prostaglandins.[21] Angiotensin II decreases renal blood flow and leads to sodium and water retention, in part by stimulating the release of vasopressin. The principal renal prostaglandins, PGE_2 and prostacyclin (PGI_2), increase renal blood flow and enhance the excretion of sodium and water, partly by opposing the actions of

vasopressin. Activation of one hormonal system immediately triggers the release of counterregulatory factors in the kidney. Although these two systems exert opposite effects, both act to preserve glomerular filtration rate.[21] Angiotensin II exerts a vasoconstrictor effect on the intrarenal efferent arterioles, while a vasodilator effect is exerted by prostaglandins on the afferent arterioles. Under these circumstances, inhibition of prostaglandin synthesis by an NSAID will lead to excessive vasoconstriction, with a subsequent decline in renal blood flow and glomerular filtration rate.[17] Consequently, acute renal failure may occur.

Oedema and sodium retention are the most common NSAID-associated adverse effects involving the kidney.[27] Although both have negligible consequences in healthy individuals, they may affect the unstable cardiovascular homeostasis in patients with heart failure. In the case of renal hypoperfusion, a decrease in glomerular filtration rate results in increased water and electrolyte reabsorption in the proximal tubule. PGE_2 decreases sodium reabsorption at the thick ascending limb of the loop of Henle by inhibiting chloride transport. Inhibition of prostaglandin synthesis under these circumstances results in increased sodium, chloride and water reabsorption in the proximal convoluted tubule, and increased sodium and chloride absorption in the ascending limb of the loop of Henle. PGE_2 also antagonises the effect of vasopressin on the collecting tubule, hence reducing water reabsorption. Therefore, by blocking PGE_2, NSAIDs cause an increase in water absorption, a reduction in urinary volume and, consequently, systemic fluid retention.[26] Water retention which is disproportionate to sodium retention may lead to the development of hyponatraemia in some patients.[28]

The antinatriuretic and vasoconstrictor effects of NSAIDs may also have important clinical implications with regard to blood pressure regulation. Several trials have studied the effect of NSAIDs on blood pressure. Results of a meta-analysis suggest that mean blood pressure is elevated by approximately 5mm Hg in patients using these drugs.[29] The hypertensive effect in this analysis was most marked in hypertensive patients who were taking medication for their blood pressure. It has been shown that the use of NSAIDs decreases the antihypertensive effects of thiazides, loop diuretics, α-adrenergic blockers, β-adrenergic blockers and ACE inhibitors.[29,30] Moreover, in patients with severe volume depletion, NSAIDs may blunt the actions of diuretics and lead to severe fluid retention.[31] Renal effects of the combination of NSAIDs with ACE inhibitors depend on pre-existing renal function.[32] Under baseline conditions, this combination has no overall effect on the kidneys. However, under conditions of renal hypoperfusion or renal impairment, the two drugs will interfere with the physiological mechanisms which serve to protect glomerular filtration rate. Hence clinicians should avoid co-prescribing an NSAID and an ACE inhibitor under these circumstances.

Suppression of prostaglandin-mediated renin release by NSAIDs may lead to a state of hyporeninaemic hypoaldosteronism, resulting in hyperkalaemia and type IV renal tubular acidosis. The degree of hyperkalaemia is usually mild, but cardiac arrest and even death may occur.[33] NSAID-induced hyperkalaemia seldom occurs in the absence of other defects of potassium homeostasis. Patients at risk are, for example, users of potassium-sparing diuretics, β-blockers and aldosterone antagonists. Patients with type 1 (insulin-dependent) diabetes mellitus with renal dysfunction and patients with renal failure are especially at high risk.[17]

Apart from the prostaglandin-mediated renal function abnormalities, NSAIDs are also associated with acute renal syndromes, such as nephrotic syndrome, acute interstitial nephritis, acute tubular necrosis, papillary necrosis and acute glomerulonephritis.[18,21] However, this is relatively rare and outside the scope of this review.

3. 'Renal-Sparing' NSAIDs

3.1 Conventional 'Renal-Sparing' NSAIDs

Efforts have been made to develop NSAIDs which do not influence renal prostaglandin synthesis, and thereby lack prostaglandin-mediated ad-

verse effects on renal and cardiovascular homeostasis.

Compared with other conventional NSAIDs, sulindac was reported to have a lower propensity for inhibiting renal prostaglandin synthesis and impairing renal function.[34-37] Because the active sulfide metabolite of sulindac is inactivated by renal oxidative enzymes, this was thought to minimise the effect of the drug on local renal prostaglandin synthesis.[34] However, clinical studies have demonstrated that this drug is capable of inducing the same renal toxicity as other NSAIDs.[38,39] Similarly, nabumetone has been postulated to have renal sparing properties.[34-36,40] Like sulindac, nabumetone is a pro-drug, which is rapidly transformed in the liver to its active metabolite 6-methoxy-2-naphtylacetic acid (6-MNA). Before being excreted in the urine, 6-MNA is metabolised to inactive metabolites which are weak inhibitors of COX.[34] However, renal failure has been reported as a consequence of nabumetone use.[41] Overall, studies assessing whether nabumetone has renal-sparing properties do not provide a definitive answer to this question.[33]

Current data strongly suggest that nabumetone and sulindac share the risks of adverse renal effects with other conventional NSAIDs. Therefore, use of these agents requires the same precautions in patients at risk of adverse renal effects during use of 'non-renal-sparing' NSAIDs. Whether these effects may be less is currently unknown. Since most studies were small and carried out in patients with normal renal function, further studies are needed before conclusions can be drawn.

3.2 Cyclo-Oxygenase-2 Selective Inhibitors

The COX-2 selective inhibitors, celecoxib and rofecoxib, were originally developed to reduce the incidence of gastrointestinal adverse effects associated with the use of conventional NSAIDs. Initially, it was assumed that these agents would also reduce nephrotoxicity, by inhibiting only COX-2, the inducible form of COX. However, renal impairment and heart failure due to treatment with COX-2 selective inhibitors have been suggested in several publications.[42-45]

Although COX-1 is expressed constitutively and is involved in homeostasis while COX-2 is mainly induced during pathophysiological processes, there seems to be a significant overlap between expression patterns and functions of these two enzyme isoforms.[46] Both are present in constitutive and inducible forms in the kidney.[47-52] The physiological roles of COX-1 and COX-2 are not fully understood. In the human renal cortex, COX-2 is predominantly expressed intraglomerularly in podocytes, suggesting a role in the regulation of glomerular haemodynamics through contraction of podocytes.[53] COX-2 expression decreases with salt depletion and increases with high-salt diet and dehydration.[54-56] Additionally, COX-2 expression is upregulated after treatment with angiotensin II receptor antagonists.[57] On the basis of the expression of COX-2 in the kidney, and the regulation of COX-2 by sodium intake and angiotensin II, it may be anticipated that COX-2 selective inhibitors exert similar effects on renal function as conventional NSAIDs. It has been suggested that COX-2 selective inhibitors spare glomerular filtration rate, which may be mediated primarily by COX-1, while effects on sodium excretion are similar to conventional NSAIDs.[58,59] However, this hypothesis was based on clinical studies in healthy individuals on a sodium-replete diet. Additional studies in healthy individuals on a sodium-restricted diet have demonstrated significant decreases in glomerular filtration rate with the use of COX-2 selective inhibitors.[60,61] Therefore, it appears that COX-2 selective NSAIDs have similar effects on renal function as conventional NSAIDs.

Data from clinical trials also suggest that rofecoxib and celecoxib have similar effects on blood pressure as the conventional NSAIDs.[62] With the exception of one study, which compared a half-maximal dose of celecoxib with a maximal dose of rofecoxib,[63] trials comparing these two agents did not show significant differences in effects on blood pressure.[62] The incidence of oedema with the use of COX-2 selective inhibitors corresponds with that of conventional NSAIDs.[62,64] Currently, data are lacking on the risk of heart failure associat-

ed with the use of COX-2 selective inhibitors. Most clinical trials have been carried out in healthy individuals. Comparative studies of these agents in patients who are at risk for NSAID-induced heart failure are needed to evaluate their safety in susceptible individuals. Since the renal effects of COX-2 selective inhibitors appear to be similar to the effects of conventional NSAIDs, administration of these drugs in patients susceptible to heart failure should be carried out with caution.

Recently, it was suggested that the use of COX-2 selective inhibitors may be associated with an increased risk of cardiovascular events, one of the major risk factors for heart failure. In an analysis of clinical trials, Mukherjee et al. concluded that the use of rofecoxib increased the risk of cardiovascular events.[65] Their conclusion was mainly based on the results of the Vioxx Gastrointestinal Outcomes Research (VIGOR) trial, in which the gastrointestinal safety of rofecoxib was compared with naproxen.[66] In contrast, data from the Celecoxib Long-term Arthritis Safety Study (CLASS), comparing celecoxib with ibuprofen and diclofenac, did not support this association.[64,67] Important differences in patient characteristics, concomitant use of aspirin and conventional NSAID comparators may partially account for the different findings between the two large clinical trials.[46] A pooled analysis by Konstam et al. of 23 phase IIb through V trials found no excess in the number of cardiovascular events with the use of rofecoxib compared with placebo or NSAIDs other than naproxen.[68] However, the data did indicate that use of naproxen was associated with a decreased risk of cardiovascular events relative to rofecoxib.

Unlike conventional NSAIDs, COX-2 selective inhibitors have no effect on platelet derived thromboxane A_2 (TXA_2) production.[59] This thromboxane causes platelet aggregation and is a potent vasoconstrictor. However, COX-2 selective inhibitors do inhibit the production of vasodilatory and antiaggregatory PGI_2. It was therefore hypothesised that the increased risk of cardiovascular events with the use of rofecoxib in the VIGOR trial may be explained by tipping the balance in favour of prothrombotic eicosanoids.[65] However, it could not be excluded that a potential antithrombotic effect of naproxen could also explain the difference between rofecoxib and naproxen. Also, by inhibiting the inflammation processes, COX-2 selective inhibitors may actually exert anti-atherogenic effects.[69] Several observational studies have recently been published that examined the relationship between the use of naproxen and the incidence of thrombotic events. Ray et al. found no evidence for a protective effect of naproxen.[70] However, three other studies demonstrated a lower risk of cardiovascular events with the use of naproxen compared with non-use or use of other NSAIDs.[71-73]

Therefore, the weight of evidence is in favour of a cardioprotective effect of naproxen. However, findings of these studies do not clarify the role of rofecoxib. More research is necessary to assess the true risk of prothrombotic cardiovascular events associated with the use of COX-2 selective inhibitors.

4. Quantitative Studies

As mentioned in the introduction, several case reports have been published in which the occurrence or exacerbation of heart failure was attributed to the use of NSAIDs.[9-13] Most of these patients had pre-existing heart disease. In view of the role of prostaglandins in the pathophysiology of heart failure, and the adverse renal effects of NSAIDs, it seems plausible that NSAIDs exert adverse effects in patients at risk for developing heart failure. So far, only few observational studies on the association between NSAID treatment and the onset of heart failure have been published (table I).

The first analytic study published was performed in a cohort of users of diuretics aged 55 years and older.[74] In this study, the concomitant use of NSAIDs and diuretics compared with the use of diuretics alone was associated with a 2-fold increased risk of first hospitalisation for heart failure. Most hospitalisations occurred within 1 month after initiation of combined therapy, with the highest risk occurring within the first days of NSAID use. As this study was performed in a cohort of users of diuretics, and the relative risk was higher in individ-

Table I. Observational studies on the association between current use of NSAIDs and heart failure

Study	Design	Population characteristics, sample size	Outcome definition	RR/OR (95% CI)
Heerdink et al.[74]	Cohort	Elderly recipients of diuretics and NSAIDs, identified in community pharmacies (10 519)	First hospitalisation with a primary or secondary diagnosis of heart failure	1.8 (1.4–2.4)
Page and Henry[75]	Case-control	Patients admitted to the emergency department of a hospital (1023)	Hospitalisation with a primary diagnosis of heart failure	2.1 (1.2–3.3)
Feenstra[76]	Cohort	Elderly recipients of NSAIDs, with one hospitalisation for heart failure, identified in community pharmacies (559)	Rehospitalisation with a primary diagnosis of heart failure	2.2 (1.4–3.4)
Merlo et al.[77]	Ecological	National patient register Sweden	Hospitalisation with a primary diagnosis of heart failure	1.08 (1.04–1.12)[a]
Feenstra et al.[78]	Cohort	Elderly recipients of NSAIDs in population:		
		without heart failure (5062)	First occurrence of heart failure	1.2 (0.8–1.8)
		with incident heart failure (85)	Hospitalisation for relapse heart failure	9.9 (1.7–57.0)

a Per increase of one standard deviation of NSAID utilisation (5.8 defined daily doses/1000 inhabitants/day).

OR = odds ratio; **RR** = relative risk.

uals with a history of heavy diuretic use, it seems likely that a number of these patients had symptomatic cardiac dysfunction preceding the date of first hospitalisation for heart failure.

Page et al. conducted a matched case-control study in two public hospitals.[75] They found a doubling of the risk for hospital admission with heart failure in patients using NSAIDs in the preceding week. The estimated odds ratio was higher for a first admission with heart failure, and increased with high-dose and long plasma drug half-life. A much stronger association was found in patients with a history of heart disease. The findings of this study are consistent with an important effect of NSAIDs in patients with left ventricular impairment.

In agreement with the above mentioned studies, are the results of a cohort study conducted in patients aged 50 years or older with a previous hospitalisation for heart failure.[76] Among patients who had received at least one NSAID prescription during the follow-up period, current use of NSAIDs was associated with a 2-fold increased risk of rehospitalisation for heart failure. In the total cohort, risk of relapsing heart failure associated with the use of NSAIDs was non-significantly increased by 41%.

To study the impact of NSAID utilisation on hospitalisations for heart failure in Sweden, Merlo et al. performed a nationwide ecological study.[77] The relative risk of hospitalisation because of heart failure was significantly increased by 8% with every increase of one standard deviation of NSAID utilisation. However, a pitfall of the ecological design is that individual events are not linked to individual exposure or covariate data. Secondary diagnoses of heart failure were not used in this study and primary diagnoses were not validated. In a recently published, large population-based cohort study in the Netherlands, among community dwelling elderly, current use of NSAIDs was not associated with an increased risk of incident heart failure.[78] Incident heart failure was defined as the first occurrence of heart failure, irrespective of whether this event led to a hospital admission. This definition is more specific than in the previously described studies, in which only hospital admissions were considered. The risk of hospital admission for relapsing heart failure was, however, significantly increased in current users of NSAIDs among persons who had filled at least one NSAID prescription at any time since first diagnosis of heart failure (adjusted relative risk 9.9).

Overall, the observational studies that have been published strongly suggest that the risk of developing symptoms of heart failure is elevated during the use of NSAIDs by patients who are susceptible to the development of myocardial decompensation. No significant association was found between incident heart failure and NSAID treatment.

5. Conclusion

Considering current knowledge of the effects of NSAIDs on: (i) renal function, and water and salt homeostasis; (ii) the important role of prostaglandins in the pathophysiology of heart failure; and (iii) evidence from observational studies, it is very likely that NSAIDs may increase the risk of developing symptoms of heart failure in susceptible patients. Patients with a history of cardiovascular disease, such as pre-existing heart failure, are particularly at risk. Therefore, NSAIDs should be prescribed to such patients as little as possible. If a prescription is justified, monitoring of renal function, adequate patient education, and increased attention for signs and symptoms of heart failure is mandatory. It is unlikely that these drugs can also induce heart failure in otherwise healthy individuals.

The actual risk of NSAID-induced heart failure is currently unknown. Few quantitative studies have been performed. These studies consistently found that the risk is at least doubled in patients with left ventricular impairment. NSAIDs are widely used, mainly among elderly individuals, who are particularly susceptible to the adverse renal effects of these agents. At the same time, heart failure is an increasingly prevalent disease. Further studies are needed to quantify the risk of NSAID-induced heart failure in patients with asymptomatic cardiac dysfunction and to assess the risks of individual NSAIDs. Differences between individual NSAIDs in the ability to induce heart failure have not yet been demonstrated, but may exist. Although several agents have been claimed to have renal-sparing properties, including sulindac and nabumetone, insufficient evidence has so far been provided to substantiate this. Overall, it appears that COX-2 selective inhibitors have similar effects on renal function as the conventional NSAIDs. Since the central mechanism by which NSAIDs influence cardiovascular homeostasis is their effect on renal function, it seems plausible to assume that COX-2 selective inhibitors may also induce heart failure in susceptible patients.

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