

Time for a comeback of NSAIDs in proteinuric chronic kidney disease?

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ABSTRACT

Before the introduction of renin-angiotensin-aldosterone system (RAAS) inhibitors in the 1980s, non-steroidal anti-inflammatory drugs (NSAIDs) were the only class of drugs available for the reduction of symptomatic proteinuria. Long-term data from those days suggested sustained renoprotective properties in proteinuric chronic kidney disease (CKD), but this potential has not been further explored, due to the adverse effects of NSAIDs, and due to the successful introduction of RAAS blockade for blood pressure control and renoprotection. The renoprotective potential of NSAIDs may seem surprising for the present generation of clinicians, as NSAIDs are well known for their adverse effects on the kidney. Interestingly, the newer selective COX-2 inhibitors (coxibs), such as non-selective (ns) NSAIDs, exert an antiproteinuric effect in CKD patients. This review discusses the role of NSAIDs as a class of drugs representing an old concept for renoprotection in the light of current insights on renoprotection. It has become increasingly clear during the last two decades, from evidence obtained almost exclusively in studies using RAAS blockade, that not only reduction of blood pressure, but also of proteinuria is a prerequisite for long-term renoprotection. Ns-NSAIDs and coxibs reduce proteinuria without reduction of blood pressure. Their possible role as an adjunct in individualised treatment strategies, particularly for individual patients resistant or intolerant to current therapy, will be discussed.

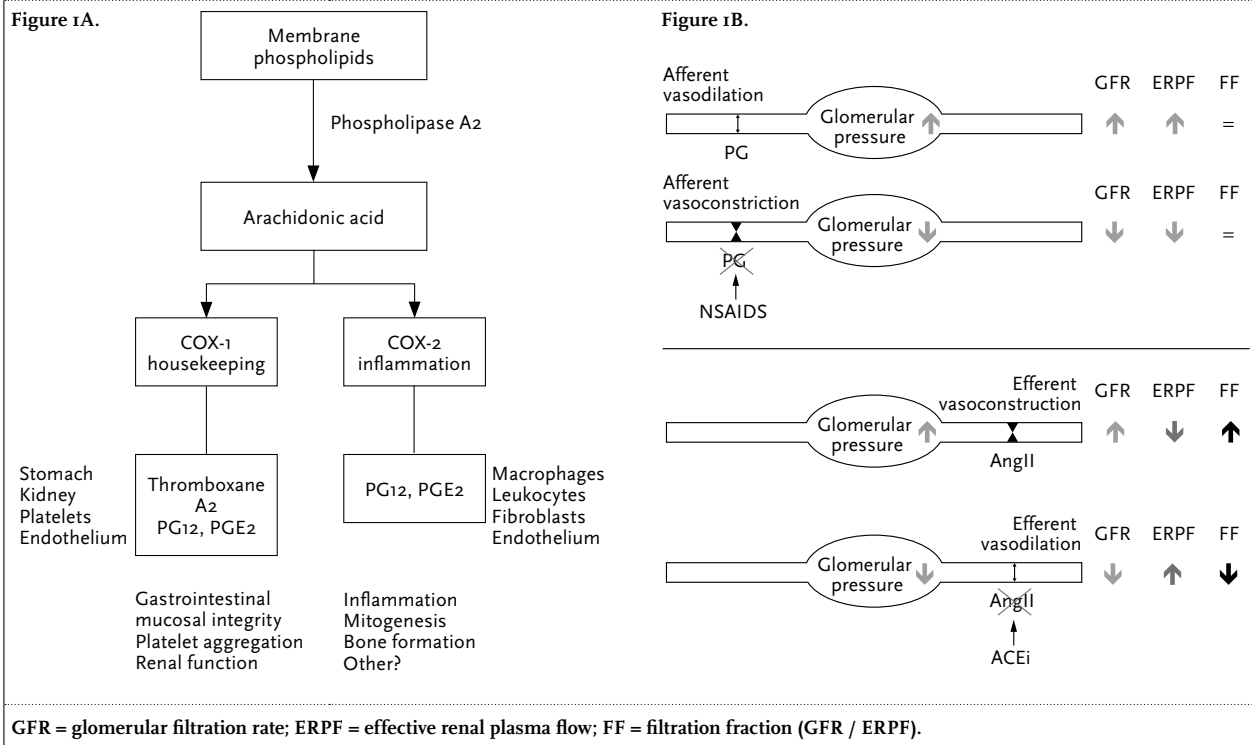
KEYWORDS

Proteinuria, nephrotic syndrome, kidney disease, NSAID, renin-angiotensin-aldosterone system, COX-2 inhibitors, prostaglandins

INTRODUCTION

Much of our current understanding of the mechanism by which drugs exert protection against progressive renal function decline is derived from randomised controlled trials (RCTs) comparing traditional antihypertensive agents with renin-angiotensin-aldosterone (RAAS) blockade in different renal populations. Reduction of blood pressure has long been recognised as a cornerstone in the treatment of chronic kidney disease, being an important prerequisite to protect against progressive renal function loss as well as against cardiovascular complications.^{1,2} RAAS blockade turned out to be particularly effective to that purpose. Interestingly, the extent of renoprotection exerted by RAAS blockade was larger than could be explained by blood pressure lowering alone, pointing towards specific renal protection. Reduction of glomerular pressure was assumed to be important in this respect (*figure 1*), alleviating hypertensive glomerular capillary damage and hence glomerular protein leakage.^{3,4} Interestingly, when more data from RCTs became available, it turned out that the available data consistently showed better renoprotection in the treatment arm with the best proteinuria reduction (usually the RAAS blockade arm), and also, within treatment groups on a specific regimen better renoprotection was seen in individuals with more effective proteinuria reduction.^{5,6} This was in line with the increasing body of evidence showing, first, that proteinuria is a main predictor of renal function loss, and second, that leaked proteins are an important pathophysiological trigger for renal tubulo-interstitial damage.³ Moreover, it became increasingly clear that proteinuria is a major risk factor for cardiovascular events.⁸⁻¹⁰ So, the ample evidence over the last three decades indicates that, in addition to adequate blood pressure control, proteinuria reduction should be an independent treatment target for renoprotection.

Figure 1. A. Substrates of NSAIDs: cyclooxygenase-1 (COX-1) and COX-2. B. Simplified reproduction of the renal haemodynamic effects of prostaglandins (PG), including PGE₂, and angiotensin II (AngII). The blocking effects of NSAIDs and ACE inhibitors (ACEi) on PG and AngII, respectively, will lead to reduction of glomerular pressure and lower urinary protein excretion. PGs affect GFR and ERPF in parallel, whereas AngII has opposite effects to GFR and ERPF, leading to alteration of FF



Current guidelines, therefore, recommend not only strict blood pressure lowering (<125/<75 mmHg) for proteinuric patients, but also reduction of proteinuria to <1 g/day, and it has been argued that an even lower target (<0.3 g/day) should be pursued.^{3,11} RAAS blockade is the cornerstone in this symptomatic approach. In specific glomerulopathies, such as idiopathic focal and segmental glomerular sclerosis, IgA nephropathy or membranous glomerulopathy, remission of proteinuria and renoprotection may preferably be induced by immunosuppressants, as reviewed previously.¹² Nevertheless, many patients depend on symptomatic therapy because immunosuppressive therapy is either ineffective or causes too many side effects. Before focussing on the role of NSAIDs in the symptomatic treatment of proteinuric CKD patients, the progression that has been made to improve current treatment schedules will be discussed in short.

INDIVIDUALISED MULTIFACTORIAL APPROACH

Despite proven renoprotective efficacy of RAAS blockade, the residual renal and cardiovascular risk of treated patients remains very high. For example, in the RENAAL

study, conducted in type 2 diabetic nephropathy, the development of ESRD was delayed by approximately 11 months only by the losartan treatment, and the event rate, albeit reduced by some 30%, was still considerably above that in the general population.¹³ To improve outcome, therefore, individualised titration regimens have been advocated to obtain control of blood pressure and proteinuria at values recommended by current guidelines. Different stepped-care 'remission regimens' were tested comprising dose titration with a single RAAS blocker, dual RAAS blockade (ACE inhibitor plus AT₁ receptor blocker (ARB)), enhancement of therapy effect by correction of extracellular volume overload (dietary sodium restriction and/or diuretic use), addition of a calcium antagonist, and lipid control.¹⁴⁻¹⁶ Ruggenenti *et al.* demonstrated the efficacy of such a 'remission regimen', showing a much slower decline of eGFR as compared with a matched historical reference group originating from the REIN study treated with monotherapy ramipril in non-diabetic proteinuric glomerulopathy.¹⁵ However, the feasibility of this strategy is limited, as many patients do not reach the treatment targets, either due to adverse events (*e.g.* hyperkalaemia, renal function impairment and hypotension) that preclude maximal titration, or an incomplete response despite maximal titration.^{15,16} Moreover, there is some evidence that

aggressive down-titration of blood pressure to levels below a systolic of 110 mmHg may be associated with a worse long-term renal outcome.⁷ These data underscore that drugs with antiproteinuric properties by a non-hypotensive mechanism deserve exploration. Furthermore, the residual renal and cardiovascular risk reflected by inadequately lowered proteinuria constitutes an unmet need, demanding additive treatment strategies.

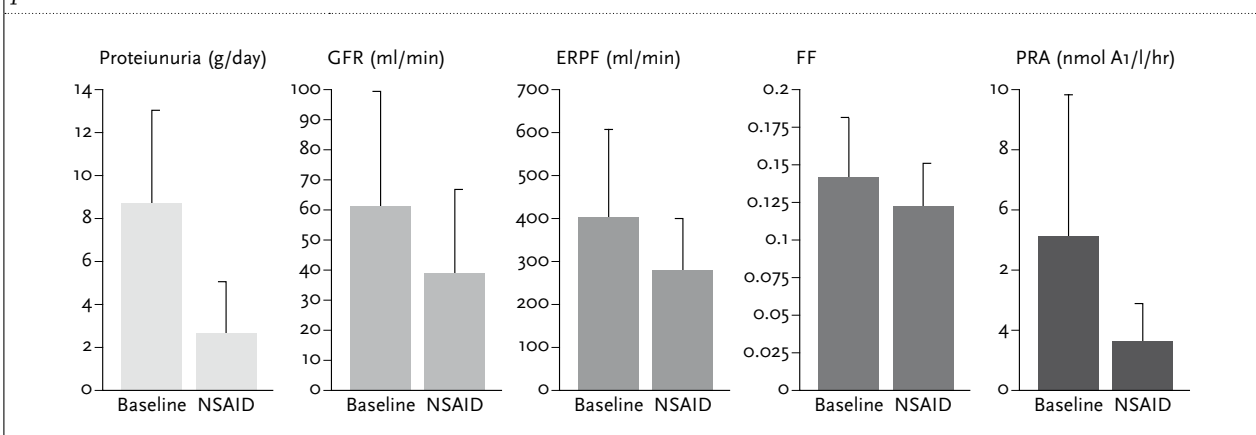
NSAIDS IN A HISTORIC PERSPECTIVE

From the mid-1950s until the mid-1980s, the potency of non-selective (ns) NSAIDs in reducing proteinuria was tested.^{17,18} Amongst others, Arisz and Donker introduced the ns-NSAID indomethacin to reduce proteinuria in steroid-resistant nephrotic syndrome.^{19,20} In those days, the renoprotective effect of proteinuria reduction was not yet known, but proteinuria was considered a target for treating nephrotic symptoms such as oedema and low serum albumin with consequent catabolic state. To improve the latter, patients generally received liberal protein diets until, in the mid-1980s, it was discovered that a low protein diet improved proteinuria and serum albumin levels.²¹ Thus, the clinical context of the early proteinuria reduction studies was quite different from today. In those early studies in heavily proteinuric patients, indomethacin, combined with low sodium diet and hydrochlorothiazide, effectively reduced proteinuria without affecting blood pressure. The antiproteinuric effect was strongly modified by the state of sodium balance, ranging from -80% during sodium depletion to zero effect during volume overload.²⁰ The reduction in proteinuria during NSAID treatment was accompanied by a proportional reduction in effective renal plasma flow

(ERPF) and glomerular filtration rate (GFR) that was more pronounced during sodium depletion as well.²² Generally, these renal effects are attributed to inhibition of renal prostaglandin production, as supported by the close correlation between reduction in urinary prostaglandin E₂ (PGE₂) excretion and the antiproteinuric effects of four different NSAIDs, indomethacin 150 mg being the most potent, followed by diclofenac and flurbiprofen, whereas sulindac had hardly any effect.²³ Prostaglandins are known to affect the kidney by modulating vascular tone, glomerular filtration, salt and water homeostasis and renin secretion.²⁴ In the injured kidney, inducible cyclooxygenase 2 (COX-2) is upregulated and newly expressed in the renal tissue (uniquely the macula densa and adjacent cortical thick ascending limbs) and accounts for the main part of PGE₂ production (*figure 1*). In the previous studies, the effects of indomethacin on ERPF, GFR, and plasma renin activity were also closely associated with the inhibitory effect on PGE₂ (*figure 2*).²⁵ Consequently, the antiproteinuric response to indomethacin has largely been attributed to these haemodynamic effects reflecting the reduction of intraglomerular pressure by predominantly afferent vasoconstriction leading to reduced glomerular leakage of proteins. Also, in diabetic nephropathy it has been demonstrated that indomethacin 150 mg reduces albuminuria up to 70%.²⁶ As in non-diabetic proteinuria, proteinuria reduction by indomethacin is accompanied by a reduction in urinary PGE₂ excretion and GFR.²⁷

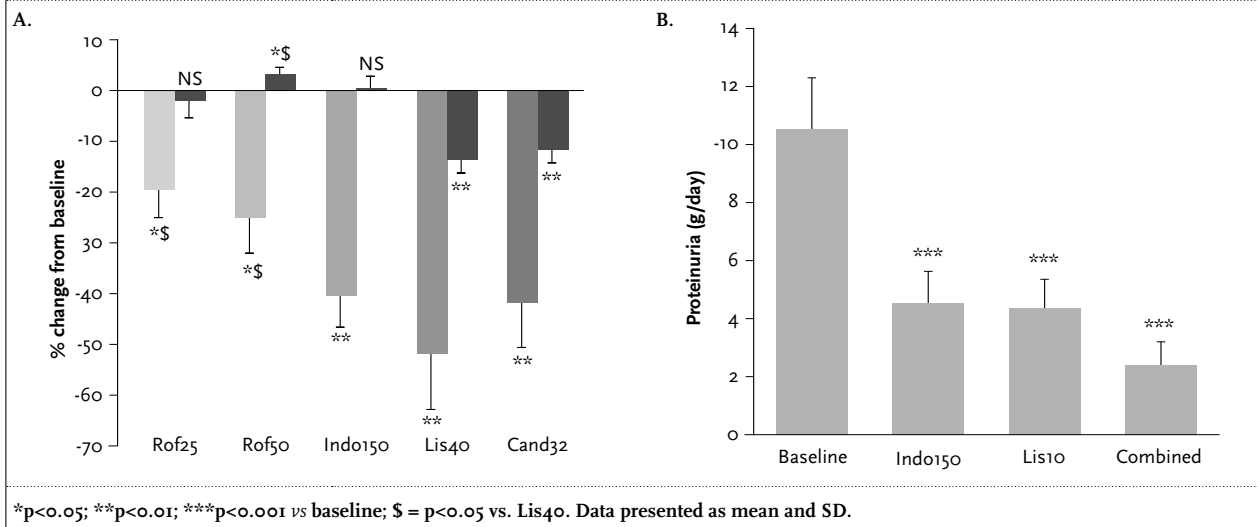
Given its high antiproteinuric efficacy in different patients, highly dosed indomethacin (150 mg daily) passed for the 'gold standard' of symptomatic proteinuria reduction, even in the early years after introduction of the first ACE inhibitor captopril. Data from a more recent head-to-head-comparison study show that both the ACE inhibitor (lisinopril 40 mg/day) and ARB (candesartan 32 mg/

Figure 2. Effects of the ns-NSAID indomethacin (150 mg/day) during salt depletion on renal parameters in 10 nephrotic patients



Data and figure adapted from Vriesendorp *et al.*²⁵ GFR = glomerular filtration rate; ERPF = effective renal plasma flow; FF = filtration fraction (GFR/ERPF); PRA = plasma renin activity; Data presented as mean and SD.

Figure 3. A. Comparison of rofecoxib 25 and 50 mg (Rof25 and Rof50, respectively), indomethacin 150 mg (Indo150), lisinopril 40 mg (Lis40), and candesartan 32 mg (Cand32) daily for their antiproteinuric efficacy in 9 proteinuric patients (data and figure adapted from Vogt L et al.²⁸)
B. Added efficacy of lisinopril 10 mg (Lis10) combined with Indo150 in 10 nephrotic patients (data and figure adapted from Heeg et al.²⁹)



day) at maximum recommended doses are more or less equipotent to indomethacin, whereas the COX-2 inhibitor rofecoxib was somewhat less potent (figure 3A).²⁸ Of note, the combination of NSAIDs and RAAS blockade has been tested as well. Indomethacin has added effects on top of adequately dosed RAAS blockade (figure 3B), indicating that these two modes of intervention act by a different mechanism.²⁹ As regards renal haemodynamics, indomethacin induces preglomerular vasoconstriction, whereas lisinopril induces postglomerular vasodilation: thus their combination leads to added reduction of glomerular filtration pressure and hence GFR and glomerular protein leakage.

Only two retrospective studies are available with data on long-term outcome with NSAIDs. The uncontrolled study by Lagrue *et al.* (1988) compared outcomes in patients treated with ns-NSAIDs with outcomes in four different series of patients not treated with ns-NSAIDs.³⁰ Patients on NSAID developed ESRD in approximately 15 vs 50% at ten-year follow-up. Another retrospective study published in the same period showed similar results in 98 nephrotic-range proteinuric patients with rather preserved renal function (defined as serum creatinine <110 µmol/l) at baseline.²² At ten-year follow-up, 31% of the patients treated with indomethacin vs 66% not treated with an antiproteinuric drug became dialysis dependent. In this study, no perfect match for baseline characteristics was established, having patients on indomethacin treatment with significantly higher proteinuria, lower blood pressure, and better preserved renal function, as compared with the control group. The suggested long-term protective

effects of ns-NSAIDs on renal function have never been tested in a controlled prospective manner, however, due to frequent non-renal as well as renal adverse effects of NSAIDs. Highly dosed indomethacin not only placed the patients at risk for gastrointestinal bleeding, but many patients also did not tolerate these doses because of adverse effects on the central nervous system, *e.g.* non-orthostatic dizziness and somnolence.^{29,31} Another unwanted effect of NSAIDs comprises water and sodium retention, elevation of blood pressure and development of oedema, potentially annulling the renoprotective effects of proteinuria reduction.³² Finally, in patients with advanced renal function impairment, the use of NSAIDs is hampered by the decrease in GFR that accompanies an effective proteinuria reduction, as well as the propensity to hyperkalaemia due to specific tubular effects.^{31,32}

PLATELET-AGGREGATING INHIBITORY AGENTS

Platelet-aggregating inhibitory agents may exert renoprotective effects as well, although they may not strictly be classified as NSAIDs. Nevertheless, these agents exert their effects by inhibiting prostaglandin synthesis for a great part, particularly by inhibition of COX-1 (figure 1). Platelet-aggregating inhibitory agents, firstly, affect platelet activity, thereby preventing endothelial dysfunction, microangiopathy and accelerated atherosclerosis, and microalbuminuria.³³ Secondly, platelet-aggregating inhibitory agents also exert their

beneficial effect by other mechanisms, such as preventing thromboxane A₂ (TXA₂)-induced vasoconstriction or reducing inflammation. So far, high-dose aspirin combined with dipyridamole, in contrast to single aspirin treatment, has shown to be effective in reducing proteinuria accompanied by a stabilising effect on GFR in the long term in two different studies.^{34,35} The observed short-term antiproteinuric effect could not be explained by acute changes in GFR or ERPF.³⁴ This may implicate a different mechanism of renoprotection as compared with ns-NSAIDs. The antiproteinuric effect of platelet-aggregating inhibitory agents seems predominantly mediated by blocking renal effects of TXA₂, whereas the renoprotective effects of ns-NSAIDs are mediated by vasomodulatory effects of PGE₂ inhibition.

COXIBS

As already mentioned, the antiproteinuric efficacy of NSAIDs relates to the extent of PGE₂ inhibition, suggesting a pivotal role of PGE₂ in the pathophysiology of kidney diseases. This is illustrated by ample evidence from murine models for renal disease.³⁶ For example, COX-2-induced production of PGE₂ induces mesangial expansion.³⁷ Furthermore, upregulation of COX-2 not only increases susceptibility to podocyte injury, but also activation of the intrarenal RAAS leading to higher angiotensin II levels, *i.e.* processes that contribute to renal scarring and the development of proteinuria.³⁸ Given the high frequency of ns-NSAID-related side effects, exploration of selective inhibition of COX-2 in renal disease was an obvious next step. Indeed, in the experimental setting coxibs had a renoprotective effect, as reviewed elsewhere,³⁶ and improved responsiveness to ACE inhibitor therapy.³⁹ Little is known of the effects of coxibs in human nephropathies. Only two studies tested the renoprotective potency of coxibs in proteinuric patients. We showed that rofecoxib reduced proteinuria by almost 30% in both diabetic and non-diabetic proteinuric patients.²⁸ Patients were studied during a standard regimen of diuretic therapy and dietary salt restriction. In an additional protocol, short-term effects of rofecoxib (25 mg and 50 mg), indomethacin (150 mg retard formula), lisinopril (40 mg) and candesartan (32 mg) were compared in a cross-over fashion (*figure 3*). Rofecoxib 50 mg had a better antiproteinuric efficacy than 25 mg, but led to higher blood pressure and body weight, presumably due to sodium retention, and decrease of renal function. Furthermore, indomethacin, the ACE inhibitor lisinopril, and the ARB candesartan had a better antiproteinuric response than both doses of rofecoxib (*figure 3A*). In contrast, Sinsakul *et al.* could not confirm antiproteinuric efficacy of the coxib celecoxib in diabetic nephropathy.⁴⁰ Their study was,

however, not designed for specific exploration of celecoxib, as it was performed on a background therapy of RAAS blockade. Also, no measures to reduce volume excess were made, no dose-titration was performed, and no comparator drug was included in the protocol. In summary, the preliminary results indicate that coxibs have potential renoprotective characteristics by proteinuria reduction without blood pressure reduction.

ADVERSE EFFECTS OF NS-NSAIDS AND COXIBS

In general, the clinical application of coxibs and NSAIDs in renoprotective treatment schedules is hampered by safety concerns. As already mentioned, the use of NSAIDs is associated with water and sodium retention, consequent blood pressure elevation and oedema as well as hyperkalaemia. Also, renal function may deteriorate considerably, although the prevalence of renal toxicity in a non-renal population appears relatively low. Renal toxicity may particularly occur in clinical settings in which maintenance of renal blood flow and filtration pressure depends on prostaglandin synthesis to ensure afferent vasodilation. This is the case during hypotension and/or decreased effective circulating volume, for instance due to heart failure, liver cirrhosis, or use of diuretics, and during age-related declines in GFR. Under those circumstances, NSAIDs can significantly decrease renal blood flow and filtration with resultant acute renal failure, usually functional and reversible upon restoration of circulating volume and withdrawal of the NSAID, but occasionally precipitating acute tubular necrosis. In addition, papillary necrosis and acute interstitial nephritis can occur in association with NSAIDs.⁴¹

It is generally believed that renal effects of ns-NSAIDs and coxibs are similar, but the non-renal effects might differ. Coxibs are considered to have a more favourable gastrointestinal safety profile, due to their selectivity for COX-2.⁴² Furthermore, coxibs are related to adverse cardiovascular effects that led to immediate withdrawal of the coxib rofecoxib (Vioxx®) from the market after results from the APPROVe trial.⁴³ The APPROVe trial studied rofecoxib in a non-renal population selected on a history of colorectal adenoma to prevent the development of recurrent neoplastic polyps, but was prematurely closed when rofecoxib at interim analysis was associated with an almost doubled risk of myocardial infarction and ischaemic cerebrovascular events. The elevated cardiovascular risk probably relates not solely to rofecoxib, but also to other coxibs, and to ns-NSAIDs. Yet, this relation seems rather heterogenic, as some reports indicate that celecoxib may not share the coxib-related cardiovascular risk elevation.⁴⁴ In particular, the elderly are at risk, also more frequently

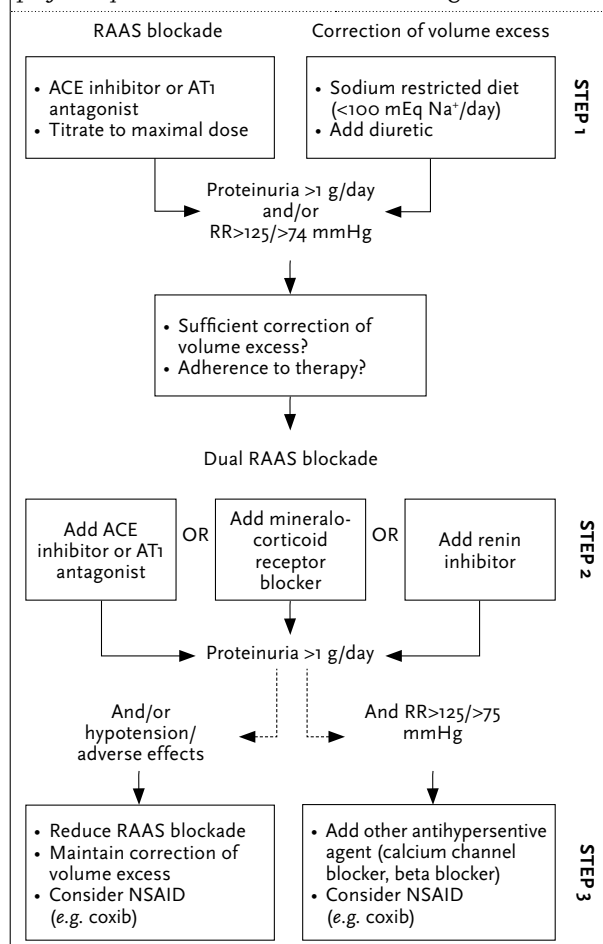
displaying congestive heart failure with a remarkable peak of heart failure exacerbations early after the start of the NSAID.^{45,46} A recent meta-analysis of 51 RCTs, comprising 130,541 patients, mainly suffering from osteoarthritis and rheumatoid arthritis, more frequently reported hypertension as a consequence of NSAID therapy.⁴⁷ Particularly, the use of coxibs as compared with ns-NSAIDs was associated with markedly raised blood pressure. Based on these data from non-renal patients, the NSAID-related elevated cardiovascular risk seems for a great part attributable to blood pressure effects and heart failure. In renal patients, where some degree of volume retention is often already present, the use of ns-NSAIDs or coxibs might therefore be unattractive in conditions where volume excess is kept unattended, as this may not only elicit the above side effects but could also annihilate the antiproteinuric response.

NSAIDS: A ROLE AS ADDITIVE TO RENOPROTECTIVE TREATMENT SCHEDULES?

Given the rationale for adjunct antiproteinuric treatment in subjects with persistent proteinuria, the adverse effects of ns-NSAIDs and coxibs deserve proper attention when considering their use for renoprotective purposes. The risks should be weighed against the risks of persistent proteinuria in patients on an already optimised regimen based on RAAS blockade. It has consistently been shown that residual proteinuria is a strong predictor of the risk for progression towards end-stage renal disease, as well as for cardiovascular complications and death. As a rule of thumb, based on post-hoc RENAAL data, one could roughly expect a twofold elevation of the risk of a cardiovascular event for each 2 grams of proteinuria.⁶ In such a weighed risk model, acknowledgement of the elevated risk related to the wide accessibility of over-the-counter NSAIDs should be included too.²⁴ Also, considering the effects of NSAIDs and coxibs on glomerular haemodynamics, which reduce autoregulatory capacity, in particular during concomitant RAAS blockade, and on renal sodium and potassium handling, such a regimen requires close monitoring of renal function, volume status and electrolytes, and should therefore only be used in dedicated nephrology settings.

If one decides to start with added NSAID therapy to RAAS blockade, patients should be instructed to seek medical attention in case of intercurrent dehydration (e.g., inadequate fluid intake, gastroenteritis, etc). Precautions to prevent the cardiovascular side effects related to volume retention apply to the use of ns-NSAIDs as well as coxibs, and consist of dietary salt restriction and/or diuretics, and inquiry about over-the-counter use of NSAIDs.²⁴ Also,

Figure 4. Proposal for a proteinuria remission regimen, including the use of coxibs. Treatment goal should be proteinuria <1 g/day and blood pressure <125/<75 mmHg. The first step consists of the start with single RAAS blockade in combination with correction of volume overload. The second step comprises addition of another RAAS blocker on top of single ACE inhibitor or AT₁ antagonist therapy, after treatment adherence has been checked. If the treatment goal is not reached or adverse events emerge (e.g. symptomatic hypotension, hyperkalaemia), the third step comprises dose tapering of RAAS blockade, addition of an antihypertensive agent from another class, and/or addition of an NSAID, preferably a coxib, under close monitoring



when the antiproteinuric response is absent or transient, one should be aware of volume retention as an underlying mechanism blunting therapeutic efficacy.¹⁴

We propose to use one of the still available coxibs as an additive measure when RAAS-inhibitor based treatment fails to reduce proteinuria sufficiently in the presence of normalised blood pressure, or leads to symptomatic hypotension. In this condition, the addition of a coxib might provide extra antiproteinuric efficacy by non-hypotensive action.

Although ns-NSAIDs could theoretically have advantages above coxibs related to their non-selective inhibition of both COX-1 and COX-2, coxibs are better tolerated by patients than highly dosed indomethacin. Also, coxibs have a lower risk of gastrointestinal bleeding.⁴² Moreover, in order to prevent such bleeding complications, application of a highly dosed combination of platelet aggregating inhibitory agents would not be attractive in remission regimens. *Figure 4* shows an individually tailored remission regimen, including correction of volume excess by low sodium intake and diuretic use, dose titration with single RAAS blockers, dual RAAS blockade, lipid control, and newer proposed renoprotective interventions, i.e. mineralocorticoid blockade and renin inhibition.

CONCLUSION

Regarding the markedly elevated cardiovascular and renal risk in patients with inadequately treated proteinuria, the antiproteinuric effect of NSAIDs may outweigh the adverse effects of NSAIDs. Clearly, the use of NSAIDs for the purpose of renoprotection can act as a two-edged sword and, therefore, more prospective evidence is needed to verify the assumption that lowest proteinuria obtained by the addition of NSAIDs leads to better long-term renal and cardiovascular outcome. For patients with a high risk of proteinuria-driven progression to ESRD, despite adequate RAAS blockade, the odds of using NSAIDs or coxibs as an additive measure to reduce proteinuria in a non-hypotensive way may be favourable. The combination of RAAS blockade with NSAIDs or coxibs for proteinuria is a powerful, but risky combination, and for its possible benefits to be realised, a dedicated setting and close monitoring are required.

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