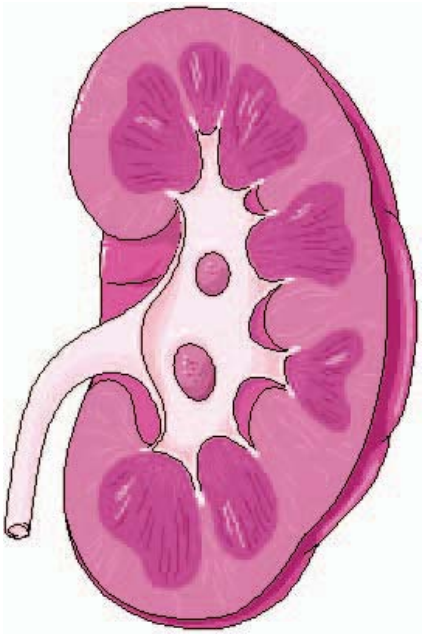
UNIVERSITY OF CALGARY
FACULTY OF MEDICINE

Renal Regulation

The Keys to Preventing Chronic Renal Failure



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As the prevalence of chronic renal failure (CRF) is increasing, the management of CRF will become a common part of the average family physician's practice. For instance, when seeing patients with CRF, family physicians need to recognise which medications can compromise renal function and those that will preserve it. The focus of this article is to highlight ways in which a physician can prevent or delay the progression of CRF.

In this article:

1. **How to preserve renal function.**
2. **Using ACEI and ARBs to prevent chronic renal failure.**
3. **Agents that threaten renal function.**
4. **How to prescribe NSAIDs to at-risk patients.**

How do you regulate the glomerular filtration rate?

The afferent arterioles of the glomeruli are regulated by two principle hormones: angiotensin II, which results in vasoconstriction; and prostaglandin (PG), which results in vasodilation (Figure 1).

The efferent arterioles are modulated by angiotensin II, which results in vasoconstriction. In times of physiologic stress, the glomerular filtration rate (GFR) is maintained by relative dilation of afferent arterioles and constriction of efferent arterioles. This is done through the activation of the renin-angiotensin-aldosterone system (RAAS). RAAS results in the production of angiotensin II, which preferentially vasoconstricts efferent arterioles leading to an increase in GFR. The reduction in effective arterial blood volume also stimulates PG production, which acts to dilate the afferent arterioles, hence maintaining GFR (Figure 1). Given this

Table 1
Keys to preserving renal function

Ways to delay the progression of CFR include:
The use of ACEis or ARBs
The treatment of hypertension
Tight glycemic control in diabetics
Other therapies for selected types of glomerulonephritis

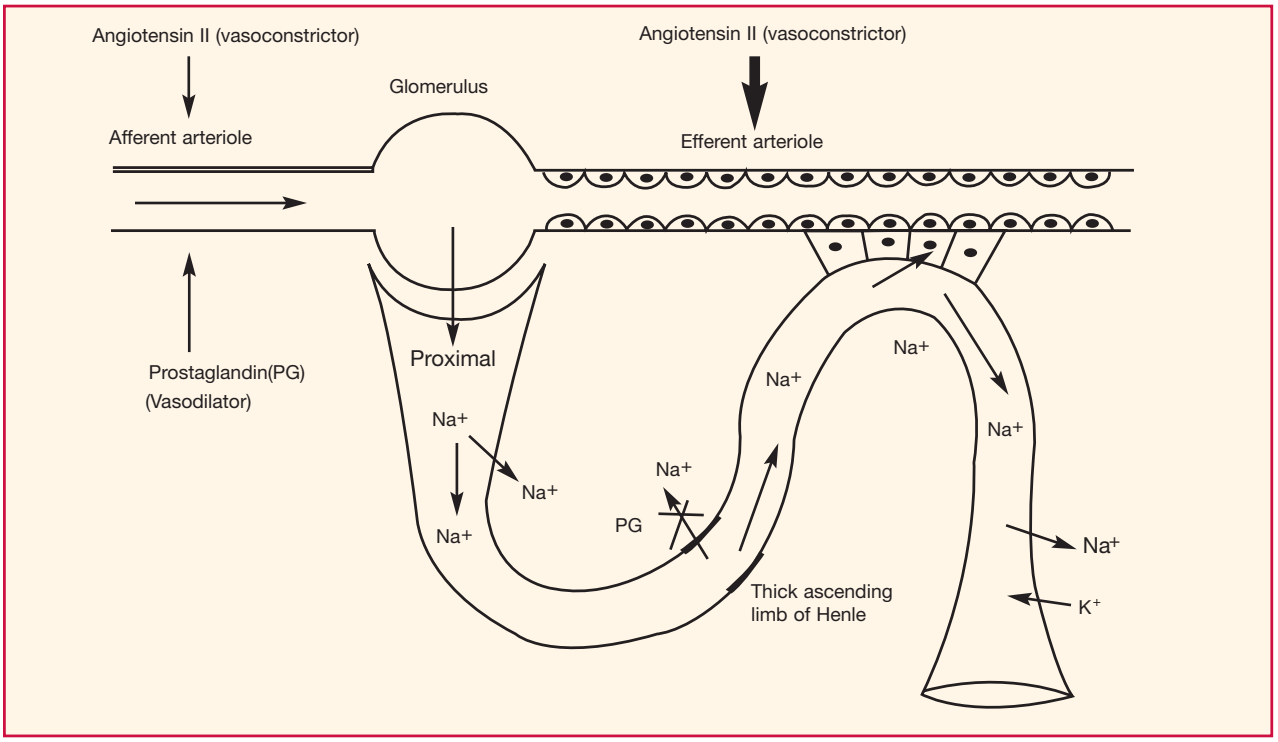

Figure 1. Regulation of glomerular filtration rate.

pathophysiologic introduction, there are several ways to delay the progression of CRF (Table 1), which will be discussed throughout this article.

What is the evidence for using ACEI and ARB?

Angiotensin converting enzyme inhibitors (ACEI) block the angiotensin converting enzyme, thus preventing the transformation of angiotensin I to angiotensin II, whereas angiotensin receptor blockers (ARBs) block the receptors for angiotensin II. The evidence that ACEI slow the progression of CRF has been replicated in several studies. For instance, one randomised controlled trial compared captopril and placebo in patients with diabetes, proteinuria, and CRF (creatinine < 221 μmol/l). The outcome was the doubling of serum creatinine levels and patients being followed for three years. Despite equal blood pressure (BP) control in both groups, 48% fewer patients treated with ACEI

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Table 2
"Prostaglandin dependent" states in which NSAIDs can cause acute renal failure

State	Possible cause
Volume depletion	Decreased fluid intake Vomiting Diarrhea Diuretics Decreased sodium intake
Decreased effective arterial blood volume	Congestive heart failure Liver disease Nephrotic syndrome
Chronic renal failure	May be occult in the elderly
Renovascular disease	Renal artery stenosis
Elderly	Loss of renal mass

reached the study's endpoint.[1] Subsequent randomised controlled trials have proven the role of ACEI in delaying progression of CRF in patients without diabetes. For example, one study demonstrated a significant difference in the ability of benazepril to reduce the progression of CRF in these patients.[2]

The evidence for ARB in delaying progression of CRF has been demonstrated in the "Reduction of Endpoints in Non-insulin dependent diabetes mellitus patients with the Angiotensin II Antagonist Losartan" (RENAAL)[3] trial and the "Irbesartan Diabetic Nephropathy Trial" (IDNT).[4] The RENAAL trial showed a significant reduction in the risk of doubling serum creatinine levels (risk reduction 25%; P = 0.006) and in the progression to end-stage kidney failure requiring dialysis (risk reduction 28%; P = 0.002) when losartan was used compared to placebo.[3] In IDNT, irbesartan was compared to both placebo and amlodipine. Similar to the results of the RENAAL trial, irbesartan therapy resulted in a 23% reduction in the progression to end-stage kidney failure when compared to placebo and amlodipine.[4]

Is it safe to start with an ACEI?

Many physicians feel that it is not safe to use an ACEI in patients with CRF for fear of worsening renal function. In fact, ACEI do decrease GFR by diminishing vasoconstriction in the efferent arterioles of the glomeruli (Figure 1). However, by preventing vasoconstriction, ACEI decrease the pressure in the glomeruli which in turn impart their long term protective effect on the kidneys. A large meta-analysis of six RCTs evaluating ACEI in patients with CRF demonstrated that ACEI are safe in patients with CRF.[5] In fact, the analysis demonstrated that ACEI safely delay the progression of renal failure in patients with CRF, as long as the acute rise in creatinine is less than 30% following initiation of the drug. Moreover, patients who had more severe renal failure had more relative benefit from ACEI than did patients with a normal creatinine.[5]

Managing a patient taking an ACEI or ARB

ACEI/ARB are very well-tolerated drugs, however, there are a few precautions that should be recognised once a patient starts the medication. The most significant side effects of these drugs include worsening renal failure, hyperkalemia, cough, and angioedema.

As described above, ACEI/ARB result in a decrease in GFR, which will lead to a rise in serum creatinine. Although expected, the rise in serum creatinine should not be higher than 30%.[5] If the serum creatinine rise is greater than 30% following the introduction of an ACEI/ARB, the drug should be discontinued as the patient may have

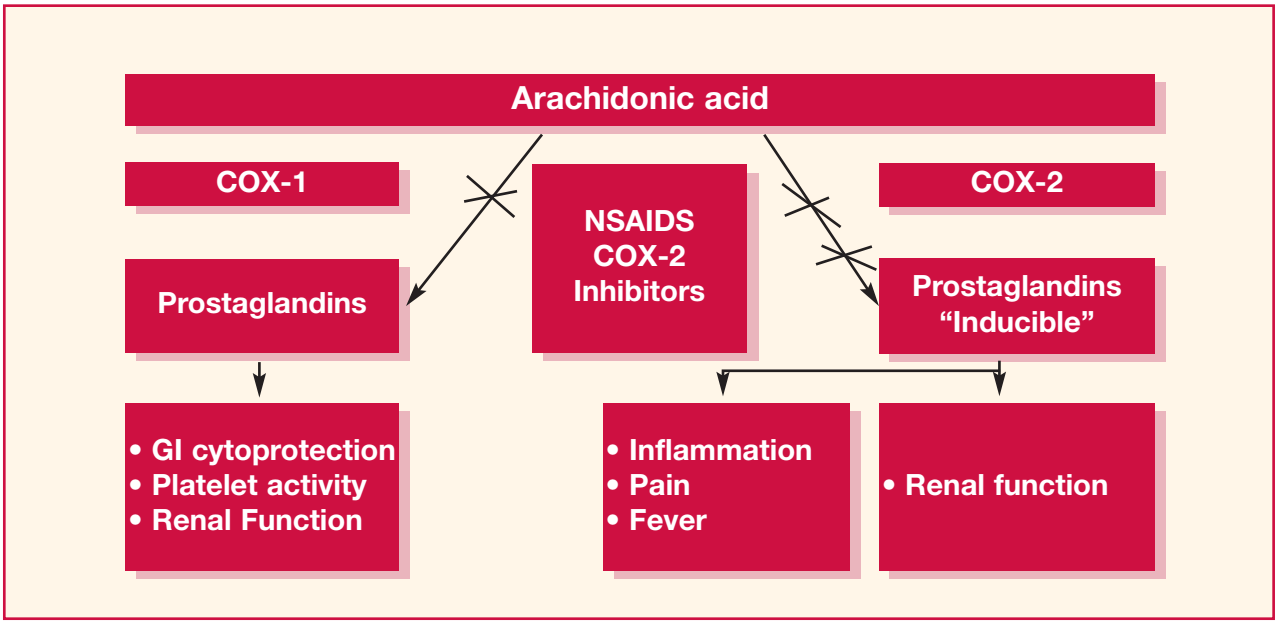

Figure 2. The effect of NSAIDS and COX-2 inhibitors on cyclooxygenase inhibition.

bilateral renal artery stenosis. At this point, a referral to a nephrologist is warranted.

Given the above, the patient's serum creatinine and potassium levels should be checked one week after starting the drug. Cough may occur after starting an ACEI because of the relative increase in bradykinins following the blockade of angiotensin converting enzymes. This does not occur with ARBs, so switching the ACEI to an ARB in the presence of cough is reasonable.

Practice Pointer

Edema and sodium retention are largely the result of the NSAID-induced blockade of the following prostaglandin-mediated properties:

- Modulation of distal tubular reabsorption of sodium and water;
- Antagonism of anti-diuretic hormone; and
- Redistribution of blood flow from cortical to juxtamedullary regions.

Finally, patient's who develop angioedema following introduction of an ACEI or ARB should have the medication stopped immediately.

The role of blood pressure

The target BP in patients with diabetes or CRF and proteinuria is 125/75 mmHg.[6,7] In patients with CRF without diabetes or proteinuria, the target BP is 130/80 mmHg.[6,7] The first-line agent in patients with diabetes, CRF, or proteinuria is an ACEI. There is growing evidence that ARBs are effective first-line agents as well. Second-line or adjunctive agents to ACEI/ARB are diuretics. Finally, dihydropyridine calcium channel blockers (*i.e.,* diltiazam or verapamil) are third-line agents since in addition to their antihypertensive effects, they have also been shown to decrease proteinuria.[6,7]

Which agents may compromise renal function?

While drugs are a common cause of renal failure in a hospital setting, they are less commonly associated with CRF in outpatients. However, certain types of medication, such as nonsteroidal anti-inflammatory drugs (NSAIDs), may worsen or provoke renal failure in patients at risk.

NSAIDs inhibit cyclooxygenase (COX) in the arachidonic acid pathway (Figure 2). COX is broken down into COX-1 and COX-2. In addition to other functions, COX-1 promotes prostaglandin (PG) production that imparts GI cytoprotection, whereas COX-2 stimulates PG production that activates inflammation and has a role in afferent arteriolar vasodilation in the kidneys (Figures 1 and 2). NSAIDs, by blocking both COX-1 and COX-2, inhibit the production of PGs in the kidneys, which are essential for afferent vasodilation and maintenance of GFR in patients with a decreased effective arterial blood volume (EABV). Table 2 provides a list of the types of patients who may have reduced EABV or who may be at risk of renal complications because of NSAIDS.

Patients with decreased EABV who are given NSAIDs develop unopposed vasoconstriction of afferent arterioles and are at risk for impairment of their GFR.[8] In addition to impairing GFR and possibly provoking acute renal failure, NSAIDs have a direct effect in worsening hypertension control (which in turn impairs renal function in the long term). NSAIDs result in hypertension by causing immediate retention of 150 mmol to 200 mmol of Na+ (Figure 1), which on average leads to an incremental rise in BP between, 3 mmHg to 4 mmHg.[9] The rise in BP is greater in patients with chronic renal failure who have "salt-sensitive" hypertension.

Edema and sodium retention are also common effects of NSAIDs, but are usually mild and subclinical. These untoward effects tend to occur shortly after the onset of NSAID therapy. The prevalence of symptomatic edema, on the other hand, is approximately only 3% to 5%. Although usually benign and of little clinical concern (typical weight gain, 1 kg to 2 kg), fluid retention can be dramatic.

In addition, edema may, to some extent, share pathophysiologic underpinnings with nephrotic

syndrome. By blocking COX-1 and COX-2, NSAIDs may shunt arachidonic acid down the lipoxygenase cascade, leading to the formation of eicosanoids that promote capillary permeability.

Another potentially serious NSAID-induced renal electrolyte abnormality is hyperkalemia. The pathophysiologic bases for this condition are twofold. First, NSAIDs tend to blunt prostaglandin-mediated renin release, leading to diminished aldosterone formation and, hence, decreased potassium excretion. Second, in the setting of diminished GFR, by opposing natriuretic and diuretic prostaglandins, NSAIDs can augment sodium and chloride reabsorption within the renal tubule, tending to diminish delivery of intra luminal sodium for sodium-potassium exchange at the distal nephron. Patients at risk for NSAID-induced hyperkalemia are in Table 3.

Table 3
Patients at risk for or prone to hyperkalemia

At risk:

- Those taking NSAIDs and potassium supplements
- Those taking NSAIDs and potassium-sparing diuretics
- Those taking NSAIDs and ACEI

Prone:

- Patients with baseline renal impairment
- Patients with cardiac failure
- Patients with diabetes
- Patients with multiple myeloma
- Patients with acute renal deterioration or impairment

Are COX-2 selective inhibitors safe?

As mentioned, PGs (which are produced by COX-2) are important in afferent vasodilation. As such, COX-2 inhibitors, which prevent afferent arteriole vasoconstriction, also result in decreased GFR in patients with reduced EABV.

Swan et al. compared the immediate effect of rofecoxib (a COX-2 selective inhibitor) 12.5 mg and indocid (a non-selective NSAID) 50 mg versus placebo on GFR in elderly patients with normal renal function and on a low salt diet. Both drugs reversibly decreased GFR by approximately 12% compared to placebo.[10]

Chronic Renal Failure

How should NSAIDs be prescribed?

Be cautious when prescribing NSAIDs to patients who are at high risk of developing renal dysfunction (Table 2). Assess the patient's degree of renal failure and do not prescribe them to patients who have a severe reduction in creatinine clearance (< 30 ml/min). In patients who have decreased EABV, use only short courses and only if there are no other alternatives. Assess the patient's electrolytes and creatinine within one week of prescribing the drug and then intermittently. Remember to discontinue the drug if the patient becomes volume depleted.

Which other agents may compromise renal function?

Other agents that compromise renal function include radiographic dyes and diuretics. Intravenous contrast for imaging may produce acute renal failure, particularly in high-risk individuals with diabetes and CRF.[11] Diuretics generally cause a small but reversible increase in serum creatinine. However, this is generally an acceptable trade off for better BP control. CME

Take-home message

Management of patients with chronic renal failure is becoming more commonplace for family physicians. By following simple principles and practices one can optimise the care of these patients. It is critical to be judicious in prescribing NSAIDs (COX-2 selective inhibitors and non-selective) and discontinue these agents in high-risk individuals. To preserve renal function in patients with CRF, initiation and maximisation of the dose of ACEI or ARB and optimisation of BP control is critical.

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Chronic Renal Failure