

THE TRIPLE WHAMMY - SAFE PRESCRIBING - A DANGEROUS TRIO

1. ACE inhibitor or angiotensin II receptor antagonist ('sartan')
2. Diuretic
3. Non-steroidal anti-inflammatory drug (NSAID) or COX-2 inhibitor ('coxib')

- ▶ AVOID THIS COMBINATION IF POSSIBLE
- ▶ BE AWARE OF THE RISK FACTORS OF RENAL FAILURE
- ▶ TAKE CARE WITH OLDER ADULTS
- ▶ ADVISE PATIENTS WHO ARE PRESCRIBED ACE INHIBITORS AND DIURETICS NOT TO 'SELF-MEDICATE' WITH NSAIDs

Triple Whammy – 'three simultaneous deleterious blows with compounded effect'.¹ The combination of medicines above can result in significant patient harm. Used individually or combined, these three medicines are involved in more than half of reported iatrogenic (treatment-related) acute renal failure cases.²

AVOID THIS COMBINATION IF POSSIBLE

The combination of all three medicines should be avoided in those with risk factors for renal failure.³ Although the focus of adverse effects from NSAIDs is usually on the gastrointestinal consequences, other risks are present such as the development of chronic heart failure, and renal impairment. Older adults and patients with co-morbidities such as heart failure or severe liver disease have an increased risk of renal failure.^{3,4}

ACE inhibitors and NSAIDs adversely affect renal blood flow and diuretics have the potential to cause dehydration. Each of these medicines affects renal function, either directly or indirectly. Further, NSAIDs antagonise beneficial antihypertensive effects of ACE inhibitors and diuretics in patients with heart failure.¹

If NSAIDs are unavoidable, use at the **lowest dose** for the **shortest duration** possible; check renal function at baseline and periodically during treatment.

Monitoring Recommendations⁶

Medication	Interaction with NSAIDs	Recommendation
ACE inhibitors	↓Antihypertensive effect ↑Risk of renal impairment Hyperkalaemia	Monitor blood pressure, weight and renal function. Monitor serum potassium
Diuretics	↓Diuretic effect ↑Risk of renal failure Heart failure may be exacerbated	Monitor blood pressure, weight and renal function
ACE inhibitors + diuretics	↑Risk of renal failure	AVOID combination with NSAIDs if possible

The Centre for Adverse Reaction Monitoring (CARM) in New Zealand received 119 reports of renal adverse reactions associated with NSAID use from January 2000 to December 2012. These included four deaths, and 12 cases that were considered life-threatening. Most of the reports were in adults over 50 years of age. The *Triple Whammy* was described in four reports. CARM encourage all healthcare professionals to report suspected adverse reactions to NSAIDs.⁷

Cases of acute renal failure attributed to NSAIDs often involve patients taking the maximum recommended daily dose or more.⁸

▶ continued

THE TRIPLE WHAMMY

2

BE AWARE OF THE RISK FACTORS OF RENAL FAILURE

Dehydration from vomiting, diarrhoea or sepsis can be a trigger for renal failure; minor illness can place susceptible patients at risk if they are taking *Triple Whammy* combinations.² Advise patients to avoid hypovolaemia by drinking plenty of water and to seek medical advice if they become acutely unwell.^{9,10}

Vomiting → hypovolaemia → precipitation of renal failure

Prescribers may also wish to **consider stopping NSAIDs** in these circumstances and to monitor renal function and serum potassium levels.¹¹

Although a risk of nephrotoxicity has been identified with these three medicines, internationally there is a lack of clear recommendations about the frequency of monitoring where this combination cannot be avoided.¹²

In general, most people aged over 75 years will require a renal function test at least once per year. This is either because of declining health, or the patient is taking medicines that require monitoring.³

TAKE CARE WITH OLDER ADULTS

Older patients are especially vulnerable to the *Triple Whammy* because they often have a degree of pre-existing renal impairment.^{2,11} Other reasons may include: sensitivity to the renal effects of NSAIDs, being prone to diuretic-induced dehydration and hypotension, and inadequate fluid intake.¹¹

Note: Anyone with renal impairment is at risk, especially if they are dehydrated.

Prescribing NSAIDs in older adults¹³

Due to the increased susceptibility of adverse effects from NSAIDs, the New Zealand Formulary recommends the following:

Osteoarthritis, soft-tissue lesions, or back pain:

- Try weight reduction first (if obese), warmth, exercise, and use of a walking stick

Osteoarthritis, soft-tissue lesions, back pain or rheumatoid arthritis pain:

- Try paracetamol first **OR** low-dose NSAID (eg ibuprofen up to 1.2g daily)
- If inadequate try full dose paracetamol **plus** a low-dose NSAID
- If necessary, increase NSAID dose **OR** use an opioid analgesic* with paracetamol

*note constipation risk

ADVISE PATIENTS WHO ARE PRESCRIBED ACE INHIBITORS AND DIURETICS NOT TO 'SELF-MEDICATE' WITH NSAIDs

Combination ACE inhibitor or angiotensin II receptor antagonists **with** diuretics (eg Inhibace Plus[®]) are useful products, but always advise patients to avoid self-medicating with 'over-the-counter' NSAIDs. This combination has been associated with a 31% increased rate of acute kidney injury; the risk of injury doubles in the first 30 days of NSAID use.¹⁴

There remains a high prevalence of NSAID use among those with relative contraindications, for example, patients who may be at risk of drug-related adverse events. A study examining NSAID use in patients with identified contraindications, found that 22% of them purchased their NSAIDs exclusively over-the-counter. Of those, 1 in 5 did not report the use of NSAIDs to clinical staff; this may reflect that these medications are considered safe by patients.⁴ Although some patients may be unaware of the risks of NSAIDs, others may choose these medicines because they offer pain relief that cannot be achieved through other means.⁴

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THE TRIPLE WHAMMY

3

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