



Avoiding the “triple whammy” in primary care: ACE inhibitor/ARB + diuretic + NSAID

Angiotensin converting enzyme (ACE) inhibitors, angiotensin-II receptor blockers (ARBs), diuretics and non-steroidal anti-inflammatory drugs (NSAIDs) all have the potential to decrease renal function. When any of these medicines are prescribed together the patient’s risk of acute kidney injury (AKI) is increased, and when all three are prescribed at once the risk is greatest. This article provides prescribers with strategies for avoiding the “triple whammy” and guidance on how to manage adverse effects if they do occur. Individualised prescribing data is also provided to allow clinicians to reflect on their practice and to identify opportunities to improve patient care.

KEY PRACTICE POINTS:

- ACE inhibitors or ARBs, with or without diuretics, are associated with an increased risk of AKI; the addition of NSAIDs significantly increases this risk
- Wherever possible, NSAIDs should not be prescribed to patients already taking ACE inhibitors or ARBs with a diuretic; also ensure that these patients know to avoid over-the-counter (OTC) NSAIDs
- If the “triple whammy” combination of medicines is necessary, baseline testing of serum creatinine and electrolytes is recommended, and patients should be advised to maintain adequate fluid intake
- Restoration of fluid balance and withdrawal of nephrotoxic medicines are the immediate goals of care if patients do develop triple whammy adverse effects

Understanding the “triple whammy”

The term “triple whammy” refers to the concurrent use of an angiotensin converting enzyme (ACE) inhibitor or an angiotensin-II receptor blocker (ARB), with a diuretic and a non-steroidal anti-inflammatory drug (NSAID), including cyclo-oxygenase-2 (COX-2) inhibitors. ACE inhibitors or ARBs and diuretics are commonly prescribed together, either as individual medicines or combination formulations, however, prescribers should remember that using these medicines together (the “double whammy”) can increase the risk of AKI. Prescribing a NSAID concurrently with an ACE inhibitor/ARB and a diuretic increases the risk of AKI considerably. Therefore, care is needed whenever a prescriber is considering the use of a NSAID in a patient already taking the “double whammy”. It is also important to educate patients taking this combination of medicines not to use NSAIDs that they have obtained themselves.



This article is available online at:
www.bpac.org.nz/2018/triple-whammy.aspx

The mechanism of the triple whammy

ACE inhibitors or ARBs generally preserve renal function. However, these medicines can also decrease glomerular filtration by causing vasodilation of the efferent renal arteriole.¹ Diuretics can also contribute to AKI by causing hypovolaemia.¹

NSAIDs are associated with an increased risk of AKI, due to blockade of the COX-2 enzyme preventing prostacyclin synthesis, which causes afferent arteriolar vasoconstriction.¹ Inhibition is maximal when steady state plasma concentrations are reached, usually after three to seven days of treatment.² The risk of AKI is highest in the first month of NSAID treatment.¹

The risk of adverse effects increases when a NSAID is added to treatment

The estimated degree of risk that patients are exposed to when taking combinations of an ACE inhibitor/ARB, diuretic and NSAID varies according to study design. A large study of over 78,000 patients found that the number needed to harm (NNH) over one year for patients taking either an ACE inhibitor/ARB or a diuretic with a NSAID (i.e. two potentially nephrotoxic medicines) was > 300; when all three classes of medicine were taken together the NNH was 158.³ Another study found that the concurrent use of either an ACE inhibitor/ARB or a diuretic with a NSAID was not associated with a significantly increased risk of AKI. However, when an ACE inhibitor/ARB, a diuretic and a NSAID were taken together, i.e. three potentially nephrotoxic medicines, the risk of AKI increased by 31%.¹

It has not been conclusively established whether occasional, short-term use (e.g. one or two days) of a NSAID in a patient taking an ACE inhibitor or ARB with a diuretic poses an increased risk. However, in the second study above, the risk of AKI was highest (nearly two-fold increased risk) within the first 30 days for patients taking the triple combination.¹

NSAIDs can counteract antihypertensive medicines and diuretics


An additional reason for avoiding the combination of an ACE inhibitor/ARB, a diuretic and a NSAID is that antihypertensive medicines and diuretics may be less effective if they are concurrently prescribed with a NSAID. When NSAIDs are taken with an ACE inhibitor, the blood pressure lowering effect of the ACE inhibitor is decreased.⁴ When NSAIDs are taken with a diuretic the effect of the diuretic is reduced and any heart failure may be exacerbated.⁴ Prescribers should also consider the increased risk of cardiovascular events associated with all NSAIDs; a risk that is higher in older patients due to their increased baseline risk of a cardiovascular event.


Identifying patients at risk of the triple whammy

Risk factors for triple whammy-induced AKI are similar to other forms of kidney injury and include:³⁻⁵

- Any stage of chronic kidney disease (CKD)
- Older age, e.g. over 75 years
- Volume depletion, e.g. due to vomiting, diarrhoea, sepsis or low fluid intake
- Māori, Pacific or Indo-Asian ethnicity
- Diabetes
- Heart failure
- Liver disease

In New Zealand, Māori and Pacific peoples are more severely affected by CKD and are therefore more likely to be vulnerable to triple whammy-induced AKI.⁶ In addition, Māori have increased dispensing rates for NSAIDs, compared to people of other ethnicities,⁷ therefore particular care is required to avoid triple whammy-induced adverse effects in this group.


 The Health Quality and Safety Commission has recently updated its Atlas of Healthcare Variation (Polypharmacy) to include data on the “triple whammy” in people aged over 65 years. For further information, see: www.hqsc.govt.nz/our-programmes/health-quality-evaluation/projects/atlas-of-healthcare-variation/polypharmacy/

 Also see: [How many patients in your practice are at risk of triple whammy adverse effects?](#)

Avoid the triple whammy by avoiding NSAIDs

Regular medicine reviews are recommended to avoid inadvertent concurrent prescribing of an ACE inhibitor/ARB, a diuretic and a NSAID. Drug interaction checkers built into patient management systems generally only search for two-way interactions, however, a warning message should be generated based on two of the three medicines, and this can be extrapolated to the triple whammy combination. When treatment with an ACE inhibitor or an ARB with a diuretic is initiated, it is helpful to highlight this in the patient’s notes to alert other clinicians who may consider prescribing a NSAID in the future.

Patients taking an ACE inhibitor/ARB and a diuretic should be warned of the risks of using NSAIDs and should be advised to avoid purchasing OTC NSAIDs, including combination products that contain NSAIDs, e.g. paracetamol and ibuprofen.

 Information for patients on NSAIDs, including a list of medicines available in New Zealand with brand names, is available from: www.healthnavigator.org.nz/medicines/n/non-steroidal-anti-inflammatories-nsaids


Pharmacists can discourage inappropriate NSAID use


Pharmacists are in a position to assess the risks of using a NSAID in patients already taking an ACE inhibitor/ARB with or without diuretics, and discuss this with the patient. It may be

appropriate in some cases to recommend paracetamol, and if an NSAID is used it should be at the lowest dose for a short period only. Patients, especially those at increased risk, who find benefit from NSAIDs and wish to continue use should be encouraged to discuss this with their general practitioner; an individual risk assessment can be performed and advice given on alternative analgesic options. Topical NSAIDs may be appropriate in some cases; the risk is lower but absorption can still occur particularly with extensive use.

Avoid oral NSAIDs when managing long-term pain conditions in patients taking ACE inhibitors/ARBs and diuretics

Joint pain is the most frequently cited reason for prescribing NSAIDs to patients taking ACE inhibitors/ARBs with diuretics.⁸ Before prescribing a NSAID for a patient with joint pain consider if an alternative option would be more appropriate. For example, for patients with osteoarthritis the first-line medicines are paracetamol and/or topical analgesia, e.g. diclofenac and ibuprofen gels or sprays or capsaicin cream.⁹ Intra-articular injections of corticosteroids can be a useful alternative to oral NSAIDs for osteoarthritic flares in some patients.¹⁰ A weak opioid, such as codeine or tramadol, may be required for some patients if pain is ongoing or severe. Exercise and physical activity can also contribute to a reduced need for medicines in osteoarthritis.¹⁰ For patients with gout, corticosteroids may be a safer option than NSAIDs for the treatment of acute flares, while colchicine may be considered for prophylaxis of gout flares.¹¹

 Further information on managing pain in patients with osteoarthritis is available from: www.bpac.org.nz/2018/osteoarthritis.aspx

 Further information on managing gout is available from: www.bpac.org.nz/2018/gout-part1.aspx

What to do if the triple whammy does need to be prescribed

If a NSAID must be prescribed to a patient already taking an ACE inhibitor/ARB and diuretic, the lowest effective dose should be used for the shortest possible duration. Renal function should be re-assessed regularly.

Advice for patients who are taking all three medicines


Maintain a good fluid intake to avoid volume depletion, particularly if feeling unwell or in hot weather (see below for advice if the patient is acutely unwell).

Avoid inadvertently taking additional NSAIDs. Educate patients about the different types and brand names of NSAIDs

that are available, e.g. ensure that they know that Nurofen and ibuprofen are the same medicine and that diclofenac and naproxen are also NSAIDs.

Discuss a “sick day” plan with the patient. If the patient becomes acutely unwell while taking the triple whammy combination of medicines, e.g. with vomiting or diarrhoea, advise them to:

- Contact their general practice to discuss whether further assessment is required
- Maintain adequate fluids; aim for pale-coloured urine
- Stop taking the NSAID and use an alternative analgesic for pain relief or fever if required, e.g. paracetamol
- Be aware of the symptoms of dehydration, such as increased thirst, dry mucous membranes, lethargy and weight loss
- Ensure they have someone to check on them regularly
- Seek medical attention immediately if their condition deteriorates

 A one-page patient information sheet highlighting the dangers of the triple whammy is available from: http://www.saferx.co.nz/Patient_info_Triple_Whammy.pdf

Monitoring for adverse effects is guided by clinical judgement

There are no guidelines for monitoring patients taking an ACE inhibitor/ARB, a diuretic and a NSAID. A pragmatic approach is to take a baseline measurement of the patient's:⁴

- Body weight
- Blood pressure
- Serum creatinine and electrolytes

A baseline measurement of serum creatinine is essential as it may be required later to diagnose AKI (see below). Serum potassium may increase with the use of ACE inhibitors or NSAIDs, particularly as renal function declines, or decrease with volume depletion.

A follow-up assessment, with repeat weight, blood pressure, serum creatinine and electrolytes, within the first month of treatment may also be beneficial, due to the increased risk of AKI during this period. More frequent monitoring of the patient is required if they become acutely unwell.

Managing triple whammy adverse effects if they do occur

The term AKI covers a spectrum from relatively small decreases in urine output and retention of waste products to complete kidney failure.¹² AKI frequently occurs as a complication of hypovolaemia or sepsis and should be suspected in all patients taking an ACE inhibitor/ARB, and a diuretic and a NSAID who are acutely unwell.¹² The symptoms and signs of AKI due to

How many patients in your practice are at risk of triple whammy adverse effects?

In New Zealand, during 2017:¹⁵

- 115,980 patients received long-term treatment* with an ACE inhibitor/ARB and a diuretic – the “double whammy”

These patients may have been prescribed a combination ACE inhibitor/diuretic, a combination ARB/diuretic or they may have been prescribed these medicines individually.

Of those who received long-term treatment with an ACE inhibitor/ARB and a diuretic during 2017:¹⁵

- 26,526 patients (23%) were also dispensed a NSAID**

Table 1 shows that the rate of triple whammy is highest in patients of NZ European ethnicity. This is likely due to the fact that they have a higher rate of dispensing of CVD medicines compared to Māori and Pacific peoples. Māori, however, have higher rates of NSAID dispensing and are more at risk of kidney injury so clinicians should ensure the risks of triple whammy medicines are not overlooked in this patient group.⁷

Table 1: The number of patients[†] dispensed an ACE inhibitor/ARB and a diuretic, and the number of patients dispensed an ACE inhibitor/ ARB, a diuretic and a NSAID, by ethnicity in New Zealand in 2017.¹⁵

Ethnicity	Number of patients dispensed an ACE inhibitor/ARB + a diuretic	Number of patients dispensed an ACE inhibitor/ARB + a diuretic + a NSAID (the triple whammy combination)	Rate of triple whammy dispensing per 1,000 enrolled patients
New Zealand European	90,221	20,321	6.9
Māori	12,965	3,028	4.5
Pacific	6,443	1,553	4.8
Asian	6,351	1,624	3.0

* Long-term treatment is defined as having at least one prescription dispensed in each quarter of 2017

** Sales of OTC NSAIDs are not included in this figure

† All age groups



Personalised prescribing reports

To see how many enrolled patients at your practice, and that you prescribed for, were concurrently prescribed an ACE inhibitor/ARB with a diuretic and a NSAID, view the online version of this article at:

www.bpac.org.nz/2018/triple-whammy.aspx

hypovolaemia include:

- Reduced urine output
- Thirst
- Lethargy
- Orthostatic hypotension
- Tachycardia
- Dry mucous membranes
- Decreased skin turgor

The diagnostic criteria for AKI are:¹³

- An increase in serum creatinine of 26.5 µmol/L or more in 48 hours; or
- An increase in serum creatinine to at least 1.5 times baseline within a 7 day period; or
- Reduced urine output (specifically urine volume < 0.5 mL/kg/h for six hours)

In practice, however, clinicians should be mindful that it may take 24–36 hours for a patient's serum creatinine levels to rise high enough to diagnose AKI.¹³

Consider withholding nephrotoxic medicines and restore fluid balance

Restoring renal perfusion is the treatment goal in patients with triple whammy-induced AKI. The patient should be advised to stop taking the NSAID and consideration given to withholding any other medicines that may impair renal function, including those requiring dose adjustments with declining renal function, e.g. metformin, gabapentin, atenolol and opiates.¹² In many situations it will be appropriate to withdraw all non-essential medicines until the patient's condition has improved and stabilised.

Fluid replacement is the simplest way of restoring renal perfusion, however, in some cases there may be underlying conditions that need to be addressed and managed, e.g. infection. The patient's renal function is the key laboratory marker when assessing treatment response.

When to seek further advice for patients with AKI

Patients with AKI that is secondary to medicine use alone and who respond rapidly to treatment, i.e. within 48–72 hours, do not usually need to be referred to secondary care.¹² Reversal of AKI can be determined clinically by checking that the patient is producing urine and repeat testing of renal function.¹⁴

Consider the need for further assessment in secondary care, or discussion with a secondary care colleague, for patients with AKI with any of the following:¹²

- No substantial improvement after 48–72 hours
- A pre-existing estimated glomerular filtration rate (eGFR) < 30 ml/min/1.73m², i.e. stage 4 or 5 CKD
- A serum creatinine three times baseline or > 353.6 µmol/L

- Anuria for ≥ 12 hours
- AKI of uncertain cause or an underlying cause requiring management in secondary care

Essential medicines should be re-started once renal function has recovered

As the patient's renal function improves, their treatment should be reviewed and essential medicines reinitiated with appropriate monitoring, e.g. renal function should be tested two weeks after reintroducing an ACE inhibitor or an ARB.¹² NSAIDs should not be prescribed in future to patients with a history of AKI. The patient's kidney function may subsequently stabilise at a higher serum creatinine level than the previous baseline and this may affect the dosing of other medicines, e.g. metformin.¹² Other potentially nephrotoxic medicines should be avoided whenever possible as patients who have had AKI are at increased risk of further episodes and progression to CKD.¹²

References

1. Lapi F, Azoulay L, Yin H, et al. Concurrent use of diuretics, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers with non-steroidal anti-inflammatory drugs and risk of acute kidney injury: nested case-control study. *BMJ* 2013;346:e8525.
2. MEDSAFE. NSAIDs and acute kidney injury. 2013;34:14–5. Available from: <http://medsafe.govt.nz/profs/PUArticles/June2013NSAIDs.htm>
3. Dreischulte T, Morales DR, Bell S, et al. Combined use of nonsteroidal anti-inflammatory drugs with diuretics and/or renin-angiotensin system inhibitors in the community increases the risk of acute kidney injury. *Kidney Int* 2015;88:396–403. doi:10.1038/ki.2015.101
4. Waitemata DHB. The triple whammy - safe prescribing - a dangerous trio. 2014. Available from: www.saferx.co.nz/full/triplewhammy.pdf (Accessed Feb, 2018)
5. Managing chronic kidney disease in primary care: a national consensus statement. 2014. Available from: www.kidneys.co.nz/Health-Professionals/CKD-consensus-statement-2015 (Accessed Dec, 2015)
6. Huria T, Palmer S, Beckert L, et al. Inequity in dialysis related practices and outcomes in Aotearoa/New Zealand: a Kaupapa Māori analysis. *Int J Equity Health* 2018;17:27. doi:10.1186/s12939-018-0737-9
7. Auckland UniServices Limited. Supply of quantitative research and analysis services: Variation in medicines use by ethnicity: a comparison between 2006/7 and 2012/13. 2018. Available from: www.pharmac.govt.nz/assets/2018-01-19-Variation-in-medicines-use-by-ethnicity-Final-Report.pdf (Accessed Apr, 2018)
8. Camin RMG, Cols M, Chevarria JL, et al. Acute kidney injury secondary to a combination of renin-angiotensin system inhibitors, diuretics and NSAIDs: 'The Triple Whammy'. *Nefrologia* 2015;35:197–206. doi:10.1016/j.nefro.2015.05.021
9. Nelson AE, Allen KD, Golightly YM, et al. A systematic review of recommendations and guidelines for the management of osteoarthritis: The chronic osteoarthritis management initiative of the U.S. bone and joint initiative. *Semin Arthritis Rheum* 2014;43:701–12. doi:10.1016/j.semarthrit.2013.11.012
10. National Institute for Health Care Excellence (NICE). Osteoarthritis: care and management. 2014. Available from: www.nice.org.uk/guidance/cg177 (Accessed Jan, 2018).
11. Hui M, Carr A, Cameron S, et al. The British Society for Rheumatology Guideline for the Management of Gout. *Rheumatology* 2017;56:1246. doi:10.1093/rheumatology/kex250
12. Oates T, Moochhala S. Recognition and management of acute kidney injury. 2017. Available from: www.prescriber.co.uk/article/recognition-management-acute-kidney-injury (Accessed Feb, 2018)
13. Ostermann M, Joannidis M. Acute kidney injury 2016: diagnosis and diagnostic workup. *Crit Care* 2016;20:299. doi:10.1186/s13054-016-1478-z
14. Chawla LS, Bellomo R, Bihorac A, et al. Acute kidney disease and renal recovery: consensus report of the Acute Disease Quality Initiative (ADQI) 16 Workgroup. *Nat Rev Nephrol* 2017;13:241–57. doi:10.1038/nrneph.2017.2
15. Ministry of Health. Pharmaceutical Claims Collection. 2018.