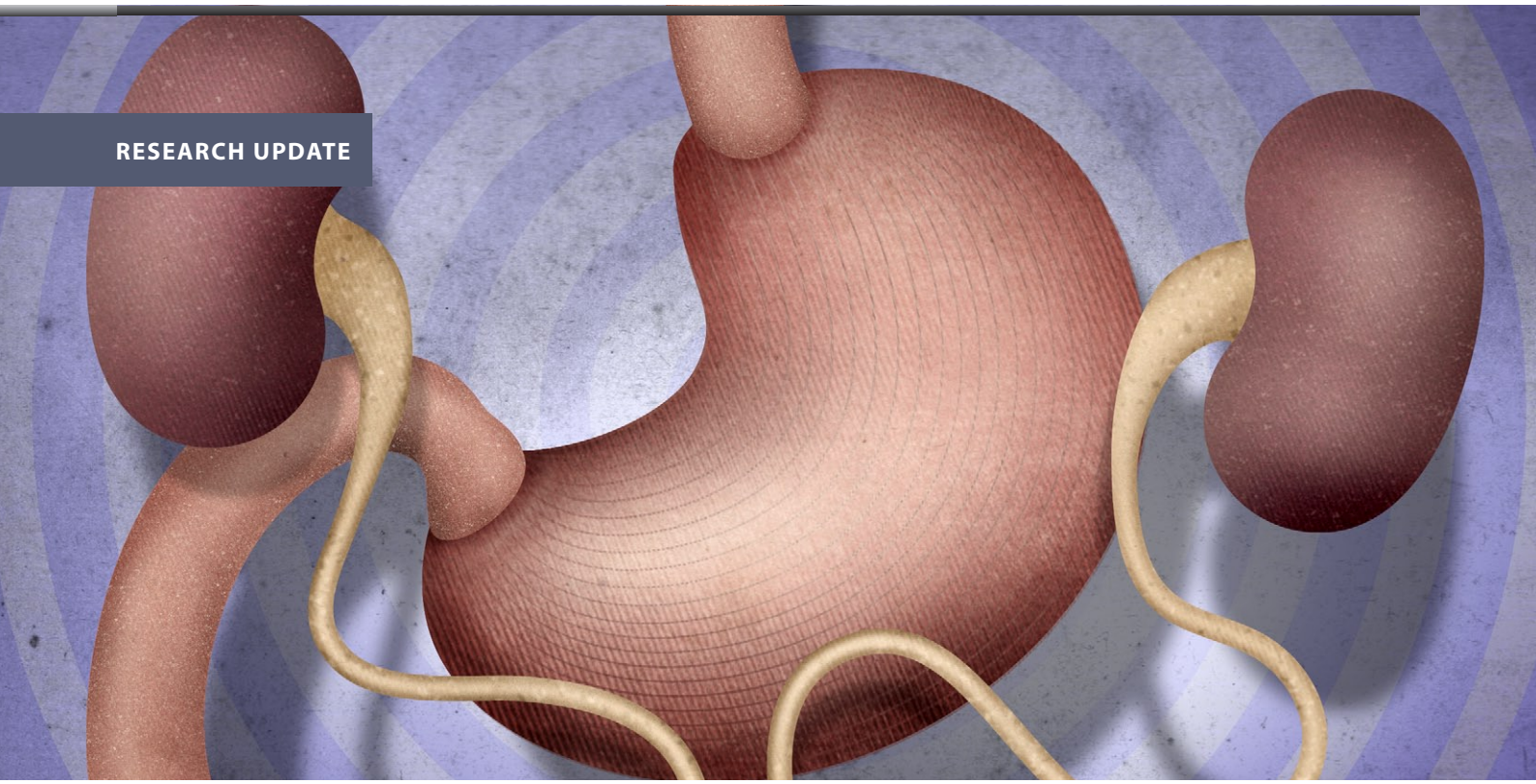
RESEARCH UPDATE



Proton pump inhibitors and the risk of acute kidney injury

KEY PRACTICE POINTS:

- The use of PPIs is associated with acute and chronic kidney injury
- When prescribing PPIs consider the patient's overall risk for kidney disease
- Maintain a high index of suspicion for kidney injury, especially during the first three months of PPI use; the risk diminishes quickly after cessation of treatment
- Features of PPI-induced acute interstitial nephritis are often non-specific and include malaise, anorexia and low grade fever in association with acute renal failure
- Prompt cessation of PPIs generally results in a full recovery of renal function, but delays in diagnosis can lead to the development of chronic kidney disease (CKD)
- PPI use should be reviewed regularly as dose reduction or withdrawal may be appropriate

Proton pump inhibitors (PPIs) are among the most frequently prescribed medicines in New Zealand. They are clinically effective and are widely believed to have few adverse effects. Recent research, however, has confirmed an association between PPI use and kidney injury. This article updates information on the safety of PPIs published in BPJ 61 (Jun, 2014).

See: **www.bpac.org.nz/BPJ/2014/June/ppi.aspx**

Proton pump inhibitors (PPIs): effective but not risk-free

Proton pump inhibitors are some of the most commonly prescribed medicines in New Zealand; omeprazole was the fourth most frequently prescribed medicine in the year to December, 2015.[1] The total use of PPIs in New Zealand is likely to be substantially higher than this as several are available over-the-counter without a prescription. This high level of use stems from their clinical effectiveness and relatively low risk of serious adverse effects. Post-marketing research reports, however, that PPIs may increase the risk of infection, fracture

and malabsorption of nutrients including vitamin B12 and magnesium.[2–4] In addition, recent research has confirmed an association between PPI use and kidney injury.[3, 5–7]

PPIs are associated with acute interstitial nephritis

Isolated case reports of interstitial nephritis in patients taking PPIs have triggered further investigation.[8] Research has now confirmed this association: patients who developed acute kidney injury (AKI), including acute interstitial nephritis (AIN), were at least twice as likely to have taken PPIs compared to those without renal disease.[6, 7] New Zealand research has also reported that patients currently using PPIs were four to five times more likely to experience AIN compared to non-users.[5] Patients over 60 years old were the most frequently affected, with approximately 20 patients in this cohort developing AIN each year per 100 000 patients taking PPIs.[5] PPI-induced AIN did not appear to be dose-dependent or related to duration of treatment.[5] This study did not report any significant relationship between interstitial nephritis and past PPI use.

Chronic kidney disease is also more common in patients taking PPIs

In addition to AKI, PPI use may cause chronic kidney disease (CKD) due to the secondary effects of AKI and hypomagnesaemia, which has been independently associated with declining kidney function.[9, 10] A large prospective cohort study in the United States reported patients taking PPIs had approximately 20–50% increased incidence of CKD compared to non-PPI users.[3]

Diagnosing acute interstitial nephritis in patients taking PPIs

Medicines are the most common cause of AIN, however, it may also be caused by infection or immunologic reaction.[6] Patients with AIN classically present with acute renal failure and a triad of fever, rash and arthralgia. This triad, however, occurs less often in PPI-induced AIN; patients are more likely to have non-specific symptoms such as malaise, anorexia and low grade fever.[6] Urine dipstick will typically show protein and white cells, and less commonly blood.[12] Laboratory investigations show acute worsening of renal function and in some cases, eosinophilia.[12]

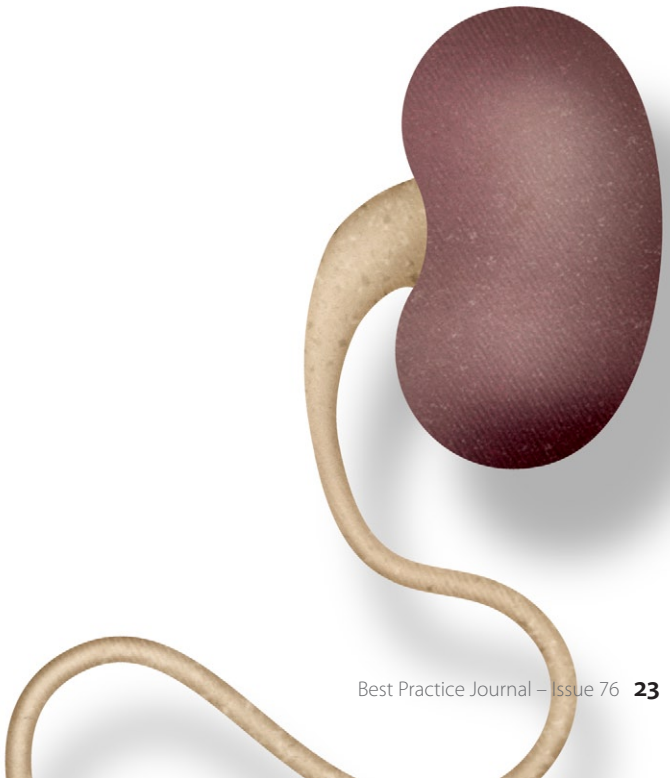
Early detection of AIN and cessation of the causative medicine is the most effective treatment.[12] Patients suspected of having AIN should be referred urgently to nephrology: 40% of these patients will require dialysis.[12] PPI-induced AIN may be less severe than AIN from other causes but recovery is often slower.[11]

Managing patients in the "real world"

While PPIs are associated with the development of both acute and chronic kidney injury, the risk is relatively low.[13] Many patients taking PPIs, however, are already at risk of renal disease as they may be older, taking NSAIDs and other nephrotoxic medicines, or have other risk factors for kidney injury. Clinicians should therefore maintain a high index of suspicion for AKI in patients on a PPI who have a rapid decline in renal function, especially during the first three months of use.[11] Baseline and monitoring of renal function may be appropriate in at risk patients.

Key features of PPI-induced AIN include non-specific malaise, anorexia and low grade fever in association with acute renal failure.[11] If AIN is suspected, request urine microscopy and renal function tests. The patient should be referred to a nephrologist for urgent review. AIN is confirmed by renal biopsy.

PPIs are widely considered to be overprescribed and this is supported by studies which show between 14 and 64% of patients using them long-term can discontinue treatment without adverse effects.[3, 14, 15] Patients may find "as required" use of PPIs sufficient to manage their symptoms. Patients taking PPIs long-term should be reviewed regularly for consideration of dose reduction or treatment withdrawal; ideally the goal of treatment is lifestyle control of symptoms with minimal reliance on medicines. Tapering is likely to be more successful than abrupt cessation, as it reduces the likelihood of rebound symptoms.[16]



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