Important New Evidence Service

In Partnership with The Centre for Medicines Optimisation at Keele University

ScriptSwitch™ Rapid Update 2 – February 2017

Under-implementation of guidance on monitoring of creatinine and potassium in those taking ACE inihibitors or ARBs

A retrospective cohort study using UK primary care data has found evidence of poor adherence to guideline-recommendations on creatinine and potassium monitoring in those taking renin-angiotensin system (RAS) drugs. Fewer than half (47%) of patients starting treatment with angiotensin converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARBs) received both baseline and post-treatment creatinine monitoring. Of these, only **9%** had undergone both pre- and post-testing within 1 month before and 2 weeks after treatment initiation. ACEI/ARBs were initiated in 7% of patients, despite baseline potassium levels above 5 mmol/L. Among the 1.4% of patients with post-treatment creatinine increases of 30% or above, or potassium levels above 6 mmol/L, treatment continued for at least 30 days in the majority.

Reference: Schmidt M, Mansfield KE, Bhaskaran K *et al*. Adherence to guidelines for creatinine and potassium monitoring and discontinuation following renin-angiotensin system blockade: a UK general practice-based cohort study. BMJ Open 2017;7:e012818

What do we know already?

- It is well established that renal function and electrolytes should be checked before starting therapy with an ACEI or ARB, with further monitoring recommended at subsequent dosage increases, and during ongoing treatment.
- Guidance on the frequency of monitoring is derived from NICE guidelines on hypertension, myocardial infarction (MI), chronic kidney disease (CKD), and heart failure; and from the UK Renal Association.
- Initial monitoring within 1-2 weeks of treatment initiation is consistently recommended.
- The frequency of ongoing monitoring needs to be tailored to the individual patient. A UKMI publication summarises suggestions for ongoing monitoring in patients with different conditions.
- NICE recommends:
  - ACEI or ARB treatment should not routinely be initiated in patients with a serum potassium level above 5 mmol/L.
  - Treatment should be stopped if serum potassium increases to 6.0 mmol/L or more, where other drugs known to promote hyperkalaemia have been discontinued.
  - If serum creatinine increases by 30% or more from baseline, in the absence of other causes, ARCI/ARBs should be stopped, or the dose reduced to a previously tolerated lower dose.
- Previous studies investigating the monitoring of renal function and electrolytes in people treated with ACEI or ARBs have found low adherence to monitoring recommendations. Studies have tended to focus on specific groups of patients e.g. those with hypertension or diabetes.

What does this evidence add?

- This study, which included a much larger UK population of ACEI/ARB users (n=223,814) not restricted by any specific diagnosis or indication, also found low adherence to biochemical monitoring recommendations.
- The results showed that about half of ACEI/ARB users had received both pre- and post-treatment creatinine monitoring within the 12 months before and the 2 months after starting treatment; however **only about a tenth** were tested within the narrower, more ideal timeframe of within 1 month before and 2 weeks after initiation.
- Following initiation of ACEI/ARBs, 1.4% of patients experienced either raised creatinine levels (*an increase of 30% or more from baseline*) or raised potassium levels (*above 6 mmol/L*), a similar finding to other studies. Whilst these creatinine and potassium levels are widely recognised as 'cut-off' values to stop (or reduce) treatment, ACEI/ARBs were continued beyond 30 days for the vast majority of these patients (80%), and beyond 90 days in over 60%. The long-term outcomes of these patients are not known.
- ACEI/ARB therapy was initiated in 7% of patients with a baseline potassium above 5 mmol/L; the routine use of ACEI/ARBs in such patients is against standard recommendations (NICE). This baseline level was also a strong predictor of subsequent hyperkalaemia (*potassium levels above 6 mmol/L*).
- Patients with hypertension or diabetes were more likely to have both pre- and post-treatment monitoring than those with heart failure, MI, or arrhythmia. Some patient characteristics increased the risk of a sudden decline in renal function, e.g. CKD stage 4, heart failure. However, not all those at increased risk were more likely to have a follow-up creatinine test within 2 weeks of starting treatment.

- Possible reasons suggested by the authors for divergence from monitoring recommendations were clinician non-adherence to ordering tests, patient non-adherence to undergoing tests that had been ordered by a GP, and lack of evidence for the clinical importance of monitoring. The authors cite a number of uncertainties with their findings; for example, blood tests carried out in other units may not have been captured, or, in cases of elevated test results, GPs may have contacted patients to advise treatment cessation ahead of having a prescription stopped. However, the findings suggest there continues to be room for improvement in the monitoring of RAS drugs.

Study details

- Retrospective cohort study using UK general practice data from the Clinical Practice Research Datalink (CPRD), linked to hospital record data from the Hospital Episode Statistics (HES) database.
- The study aimed to evaluate adherence to guidance on serum creatinine and potassium monitoring, and treatment discontinuation, in patients starting ACEI/ARB therapy.
- Definitions:
  - Baseline creatinine and potassium levels - the single most recent measurement within 12 months of the date of the first ACEI/ARB prescription.
  - Post-initiation monitoring - that undertaken within 2 months of drug initiation.
  - Testing was further categorised into within 1, 3, and 12 months before initiation, and within 2 weeks, 1 month and 2 months post-initiation.
- The investigators also explored whether any patient characteristics were associated with frequency of monitoring and a decline in renal function, i.e. age, gender, calendar period of ACEI/ARB initiation (2004-2008 and 2010-2014), socioeconomic status, smoking, alcohol intake, body mass index (BMI), CKD, cardiovascular morbidities (heart failure, MI, hypertension, peripheral arterial disease, arrhythmia), and diabetes.

Participants:

- Patients aged ≥18 years initiated on ACEI or ARB treatment for any indication between 1 January 2004 and 31 March 2014.

Outcomes and results:

Creatinine monitoring - how many were monitored and when?

- Of 223,814 new users of ACEI/ARBs, 47% had both baseline and follow-up creatinine tests (i.e. within 12 months before, and up to 2 months after treatment initiation), 28% had only a baseline test, 15% had only follow-up tests, and 10% had neither baseline nor follow-up tests.
- The median number of days between baseline monitoring and first prescription date was 40 days (Interquartile range 12-125 days).
- 34% of patients had a creatinine baseline test within 1 month prior to ACEI/ARB treatment initiation; 52% in the 3 months before, and 76% patients up to 12 months before treatment started.
- Follow-up creatinine testing was undertaken within 2 weeks of treatment initiation in 29% of patients, within 1 month in 51%, and within 2 months in 62%.
- 9% of patients had both baseline and follow-up creatinine tests within the more desirable time frames (up to 1 month before starting treatment and within 2 weeks after starting treatment). This proportion increased to 14% when the follow-up period was extended to 3 weeks.
- Monitoring did not improve in more recent study calendar periods.
- Were some patients more likely to receive creatinine monitoring? Compared with patients without any monitoring, patients with both pre- and post-testing were more likely to have hypertension (76% *vs.* 61%), or diabetes (20% *vs.* 7%), but less likely to have heart failure (4% *vs.* 7%), MI (4% *vs*. 18%), or arrhythmia (7% *vs*. 10%).

Changes in creatinine and/or potassium after treatment initiation

- Of the 21% of patients with a follow-up test within 2 weeks of starting treatment (and a baseline result for comparison), 1.2% experienced a creatinine increase of ≥30%, and 0.4% a potassium level above 6 mmol/L (1.4% experienced one or both). Of these patients 80% continued with drug therapy beyond 30 days of the monitoring date (i.e. they were issued with another prescription), and 60% who had hyperkalaemia and 65% who had a raised creatinine continued treatment for beyond 90 days.
- Patient characteristics associated with an increased risk of creatinine elevations of 30% or greater at the first post-initiation test were: female gender, age above 70 years, CKD stage 4, heart failure, peripheral arterial disease, MI, and hypertension. Some of these groups were more likely to have a follow-up test within 2 weeks of treatment initiation (age above 70 years, CKD stage 4, and those with peripheral arterial disease or heart failure).
- Factors associated with an increased risk of having a raised potassium level (above 6 mmol/L) at the first post-initiation test were: heart failure, CKD stages 3 or 4, and baseline potassium above 5 mmol/L. This baseline potassium (above 5 mmol/L) was associated with a six-fold increased risk of subsequent hyperkalaemia (Odds Ratio [OR] 6.68, 95% CI 4.94 to 9.02). Among those with baseline monitoring data, 7% started ACEI/ARB therapy with a potassium level above 5 mmol/L.

Level of evidence: Level 2 (limited quality patient-oriented evidence) according to the SORT criteria.
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