Dose optimisation following myocardial infarction

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Dose optimisation of medicines for secondary prevention of MI provides evidence-based benefits, but studies show that ACE inhibitors and beta-blockers are prescribed at suboptimal doses on discharge and are not appropriately up-titrated thereafter. Here we look at the reasons why and the possible solutions.

Optimum doses of secondary prevention cardiac medicines need to be achieved post-myocardial infarction (MI) to derive evidence-based benefits, including reduction in mortality, less hospital readmission and better symptom control.\textsuperscript{1–3} While intensive statin therapy can be started at high-target doses, ACE inhibitors and beta-blockers require up-titration to reach target or maximum tolerated doses.\textsuperscript{1–3}

Ideally dose titration should occur before discharge from hospital, but this does not always happen because of a lack of knowledge of the hospital prescriber, contraindications to dose titration or short duration hospital admissions.\textsuperscript{4}

In the event of partial dose titration on discharge, then communication to GPs should ensure that a plan is in place to continue titration post-discharge.

Evidence for lack of dose titration

Studies on prescribing post-MI show that between 60 and 90 per cent of patients are receiving each discharge medication as recommended by NICE.\textsuperscript{5–8} Recent audits indicate that this does appear to be increasing.\textsuperscript{5} According to the 2013 Myocardial Ischaemia National Audit Project (MINAP)\textsuperscript{9} the use of ACE inhibitors and beta-blockers for secondary prevention on discharge remains high, 95 and 97 per cent respectively. However, various studies and audits continue to show that ACE inhibitors and beta-blockers are prescribed at suboptimal doses on discharge, and not appropriately up-titrated to target doses or maximum tolerated doses thereafter.\textsuperscript{4,10} In its updated guidance, NICE (2013) highlights that since the publication of the 2007 guidance, there have been apparent inconsistencies in the speed of ACE inhibitor titration and often clinically effective doses are not reached at the time of hospital discharge and in the community.\textsuperscript{11}
One of the recommendations of NICE to overcome the problem of lack of dose titration is to fast titrate the ACE inhibitors in hospital. This recommendation was based on studies that examined fast versus slow up-titration regimens of ACE inhibitors. In the Pfeffer et al study, ramipril was up-titrated to 10mg/day over a three-day period.

A recent small audit (n=37) on the cardiology wards at Leeds Teaching Hospitals NHS Trust, which will be published in full at a later stage, showed that 40 per cent of patients who were started on ACE inhibitors and 43 per cent of patients on beta-blockers could have been up-titrated to higher doses before discharge. Six months’ follow-up of those patients post-discharge revealed that almost 50 per cent did not have any up-titration of their ACE inhibitor doses, nor did 85 per cent of beta-blocker doses get up-titrated in the absence of any obvious clinical reason (eg low BP or heart rate).

Benefits of dose optimisation

In heart failure, a lack of dose titration can lead to treatment failures with likely consequences of increased mortality and hospital admissions.

The prognostic benefits for the use of ACE inhibitors and beta-blockers post-MI are based on various studies such as Acute Infarction Ramipril Efficacy (AIRE), Carvedilol Post-Infarct Survival Control in Left-Ventricular Dysfunction (CAPRICORN) and other secondary prevention studies. These trials used higher doses of these drugs and doses were up-titrated to specific target doses. It is for that reason that NICE and other guidelines recommend up-titration of ACE inhibitors and beta-blocker doses, as lower doses may not confer the same benefit seen in these trials.

NICE guidance

NICE guidance on secondary prevention of MI recommends offering all people who have had an acute MI an ACE inhibitor, dual antiplatelets (aspirin plus another antiplatelet), a beta-blocker and a statin.

NICE states that the ACE inhibitor dose should be up-titrated at short intervals (eg every 12 to 24 hours) before the person leaves the hospital until the maximum tolerated or target dose is achieved. If not achieved during the hospital stay then dose titration should be completed within four to six weeks of hospital discharge. Plans for up-titrating the beta-blocker until the maximum tolerated or target dose is achieved should be communicated in the discharge summary.

The discharge summary should include: confirmation of the diagnosis of an MI, results of investigations, incomplete drug titrations, future management plans and advice on secondary prevention.

NICE also advises that a clear management plan should be available to the person who has had an MI and the GP including: details and timing of any further drug titrations, and monitoring of both BP and renal function.

Post-MI patients are supported for limited period through outpatient appointments and cardiac rehabilitation. However, most patients receive little support and mechanisms are not normally put in place to dose-optimise medicines and support adherence. Even if secondary care support is available, after a period of time patients are ‘discharged’ back to GP care and more intensive support can stop. If dose optimisation has not occurred by this point then there is a danger it will not happen.

Why doesn’t dose optimisation occur?

There are a number of theoretical reasons that can be postulated as to why dose titration does not occur, but little empirical evidence.

Adverse effects

Legitimate reasons as to why doses cannot be increased include low BP on higher doses or other adverse effects, such as bradycardia from higher doses of beta-blockers, or clinically significant decreases in renal function with higher doses of ACE inhibitors.

Lack of knowledge

A simple explanation might be that GPs lack knowledge about the benefits of dose titration. However, in other conditions lack of knowledge has been shown not to be a barrier.

Collusion of anonymity

During the period after an MI when the patient is still being seen as an outpatient, there may be confusion between the specialist and the generalist as to whose responsibility it is to make dose changes.

Lack of communication between secondary and primary care

While the discharge summaries from the hospital may include the correct secondary prevention medicines, as shown in MINAP data, they do not necessarily include clear instructions for the GP to up-titrate the ACE inhibitors and beta-blocker doses to target or maximum tolerated doses. Similarly, required follow-up monitoring should be highlighted on the discharge summary. This is a clearly emphasised NICE recommendation.

Follow-up plan

A more likely explanation as to why dose titration does not occur is the lack of a follow-up plan. To enable dose titration to occur, a number of steps are required. Firstly the BP, heart rate, and urea and electrolytes (U&Es) need checking. When results are obtained a higher dose can be prescribed accordingly. The patient then needs to know that a higher dose has been prescribed. This cycle needs repeating until an evidence base or maximum tolerated dose is achieved.

A failure in any stage will result in dose titration stopping; the more stages present the less likely it is that dose titration will occur. For instance, if a practice nurse takes a blood sample, the GP will see the results but may be unaware that a dose titration is required. Alternatively the cycle might be broken by a patient failing to turn up for a test or a follow-up GP appointment.

Solutions

Fewer dose titrations

The simpler the process, the more likely that evidence-based doses will be achieved. Ideally the patient’s doses would be optimised before discharge.
from the acute admission as close daily monitoring is possible during their hospital stay. Evidence from clinical trials that used ACE inhibitors showed that doses were usually up-titrated to target doses or maximum tolerated doses in a very short period in secondary care.

For example, the AIRE study\(^1\) showed an observed risk reduction of all-cause mortality of 27 per cent (95% CI, 11 to 40; \(p=0.002\)) using the following protocol:

- Patients initially received 2.5mg of ramipril (or placebo) twice daily. If tolerated for two days the dose was increased to 5mg twice daily thereafter. If the higher dose was not tolerated, patients were discharged on 2.5mg twice daily.
- Ramipril 1.25mg was provided for patients who could not tolerate the initial 2.5mg dose. After two days, the dose was increased to 2.5mg twice daily and then 5mg twice daily.

Based on the aforementioned, it is apparent that trials had usually used only two or three up-titrations before reaching target dose or maximum tolerated doses. A similar protocol can be implemented in practice and made available to all prescribers in hospitals. The AIRE trial excluded patients who could not tolerate doses less than 2.5mg twice daily. The protocol stated that patients who were unable to tolerate at least 2.5mg twice daily of ramipril should be withdrawn from the study. The protocol did not allow discharge of a patient on the low dose of 1.25mg twice daily.

The Leeds Teaching Hospitals NHS Trust’s cardiology department has recently adopted a similar protocol, which helped prescribers to prescribe more optimal doses of ACE inhibitors post-MI.

**Improve practice protocol**

Patients currently see different staff members for different parts of the pathway for dose titration, e.g. nurse for bloods, GP for prescribing. If a current barrier is an understanding of each team member’s responsibility a protocol might help. The protocol would detail the team members’ responsibilities including communication with each other and the patient. To simplify this process, nurses might for example take the tests and also make the dose adjustments (under protocol) once the results are available, and communicate the change to the patient.

**Improve quality of discharge summaries**

More hospitals are now using electronic discharge systems, which can be programmed to automatically insert a request to up-titrated doses of ACE inhibitors and beta-blockers as appropriate. A similar automatic statement can be included about monitoring.

Local protocols can clearly state the need to detail dose titration and monitoring plans for secondary prevention medicines. All discharge prescriptions are validated by clinical pharmacists who can police the quality of the instructions given about secondary prevention medicines post-acute coronary syndrome (ACS) and amend them accordingly to ensure that they meet agreed local protocols.

In Leeds Teaching Hospitals NHS Trust’s cardiology department, cardiology pharmacists have adopted this practice, which led to better quality electronic discharge advice notes. The impact of this practice on dose titration is currently being evaluated.

**Patient ownership of the process**

The patient is the ‘common denominator’ in the dose titration pathway. A patient-hand-held or electronic record would help the patient to manage the pathway by giving them responsibility to ensure tests (e.g. U&Es) are taken and a prescriber is then communicated with (face to face or over the phone) to increase the dose.

Patients should be informed of the intended therapeutic care plan. Many patients are discharged without being informed that their ACE inhibitors or beta-blocker doses should be up-titrated. Empowering patients with more detail of their care plan should increase the likelihood of optimising therapy.

**Conclusion**

ACE inhibitors and beta-blockers are routinely initiated after MI; however, lack of dose titration to achieve evidence-based doses is a common problem. A number of interventions could be made to increase dose titration such as fewer dose titrations, better communication of care plans and patient involvement.

**References**


**Declaration of interests**

None to declare.

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