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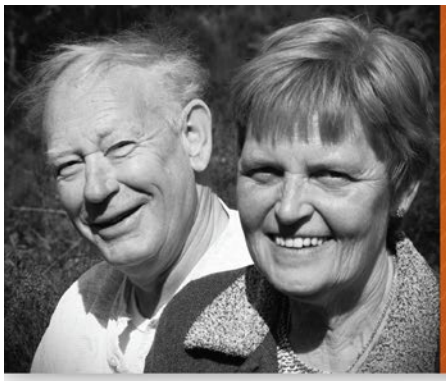
Veterans' MATES



Therapeutic Brief 36

www.veteransmates.net.au

Topic 36: Statins: keeping the benefits, reducing the risks

In 2011, one third of the Australian veteran population were using statins. More than 80% receiving statins were initiated on a high potency statin while 33% were initiated on a high potency, high dose statin.[1]

Because the elderly are more likely to receive the most medicines, have multiple co-morbidities and may have altered pharmacodynamics, they are at a particularly high risk of medicine-related adverse events.[2]

There is evidence that statins significantly decrease Low Density Lipoprotein Cholesterol (LDL-C) levels, a powerful risk factor for cardiovascular disease, across broad populations and risk groups.[3-7] The benefits of statins appear greatest in those people at the higher levels of cardiovascular risk.[5,7]

Greater reductions in LDL-C levels due to statins are associated with greater reductions in cardiovascular events.[5,8] This may drive the use of more intensive statin therapy, which can come at a risk of adverse events. A clinical judgement should be made to consider the balance between the risks and benefits of treatment, especially in older people and in those receiving statins for secondary prevention at high risk. Quality of life and the appropriateness of treatment targets for individuals should also be considered.[7]

This therapeutic brief outlines steps to minimise adverse effects associated with statin therapy.

Asymptomatic mildly elevated liver enzymes (predominantly ALT) are commonly observed with statin use, are dose dependent and generally resolve with a reduction in dosage.[9] Statins are more often associated with a variety of mild to moderate muscle-related complaints such as aches and pains, cramps and weakness which represents a clinically important contributor to poor quality of life and noncompliance. Evidence suggests most incidences of serious muscle-related adverse effects are linked to risk factors that increase either the statin systemic bioavailability or the sensitivity to increased statin blood levels.[10]

Box 1: Risk factors for developing myopathy and rhabdomyolysis[3,9,10]

High dose or high potency therapy
Concomitant interacting drugs
Advanced age (80 years) and frailty or multiple diseases
Pre-existing muscle disease
Severe inter-current illness (infection, trauma, metabolic disorders)
Renal impairment

Minimising adverse events, even mild muscular symptoms, by ensuring the dose and potency of the statin chosen is appropriate for the individual patient will promote better adherence and maximise the benefits of long-term therapy.[3] When prescribing combination products that include a statin, the dose and potency of the statin should also be appropriate for the patient. Specific LDL-C targets are intended as a guide only especially if they cannot be easily achieved without problematic effects: some benefit will be gained with any reduction in LDL-C levels.[7]

Consider the following questions if your patient is experiencing any unexplained muscle-related aches and pains or weakness.

Inside

Key questions to minimise risks associated with statin therapy

Is your patient experiencing unexplained muscle aches and pains or weakness? If so:

- Is your patient elderly?
- Is high intensity statin therapy necessary?
- Are interacting medicines prescribed?
- When was the last clinical review undertaken?

Consider: Does therapy need to be reviewed in your older patient?

The *Guidelines for the management of Absolute cardiovascular disease risk* recommend those patients at high risk of cardiovascular disease receive statins unless contraindicated or clinically inappropriate. Those patients at low risk are not routinely recommended to receive statin therapy, but consider statins for patients with moderate risk if 3-6 months of lifestyle modification does not reduce cardiovascular risk. However, statin therapy may not be appropriate in all situations.[7]

Although all older people are at high cardiovascular risk, people over the age of 80 years are not well represented in statin trials, raising uncertainty as to the risk/benefit ratio in this group.[2,11] Ageing is often accompanied by functional decline, sensory impairment, frailty, cognitive and renal impairment and multi-morbidity.

Hence, it is important to consider quality of life and life expectancy when prescribing statins in the very elderly.[11] Discuss the patient's wishes, expectations and goals with the patient when making treatment decisions.[2,7,11]

Symptoms associated with muscle-related adverse events may be difficult to differentiate from muscular complaints commonly experienced by older people. This may make it difficult to determine whether or not the symptoms are associated with the statin.[10]

There is recent evidence to suggest that musculoskeletal complaints such as aches and pains and injuries are more common amongst physically active statins users.[12] If your patient exercises or is physically active and is experiencing aches and pains, consider lowering the dose and/or the potency of the statin.

Muscle-related effects may range in severity from mild to severe and potentially fatal. Ensure patients at high risk of developing muscle-related adverse effects are aware of early warning signs and encourage them to report any unexplained muscle aches and pains or weakness, especially if accompanied by fever and general malaise.[10]

If your patient is elderly or frail, consider:

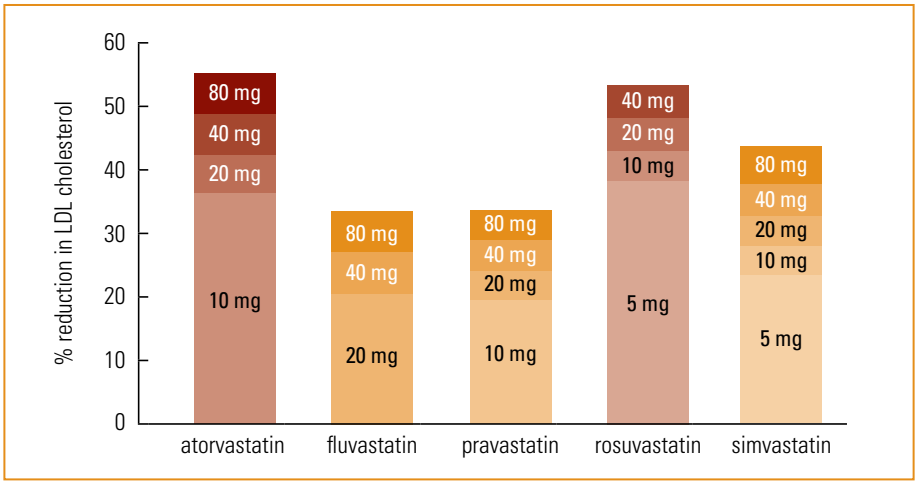
- reviewing the statin therapy
- ensuring your patient is aware of early signs and symptoms of muscle-related adverse effects
- lowering the dose and/or potency
- ceasing the statin.

Consider: Is high dose or high potency therapy necessary?

While intensive dose statin therapy has been found to produce superior treatment effects, high dose therapy may not be appropriate, even for those at higher cardiovascular risk.[8,13] Because adverse effects appear to be dose dependent and more than 80% of the LDL–C lowering effect of statins is achieved with 50% of the maximum dose, give careful consideration to the risks and benefits when prescribing high dose statins.[9,14] Reserve high doses of statins for patients who remain at high cardiovascular risk after failing to achieve target lipid levels on lower doses and when benefits are expected to outweigh potential risks.[3]

Statins lower serum lipid levels to differing extents.[15,16] Atorvastatin and rosuvastatin are considered the most potent of currently available statins.[17] Caution is advised when prescribing simvastatin 80 mg as the risk of muscle-related adverse effects is greater compared with other statins with similar LDL-C lowering efficacy.[18]

Graph 1: Effect of statins and their doses on reduction of LDL-C levels



Adapted from NPS News 71 2011. Managing lipids, reducing cardiovascular risk, with permission of National Prescribing Service.[13,14]

If your patient is taking a high dose or high potency statin, consider:

- the anticipated clinical benefit against the increased risk of myopathy
- lowering the dose
- reducing the potency.

Consider: Are interacting medicines prescribed?

Many people taking statins also take other medicines, some of which affect the clearance of the various statins by differing pathways. Potential serious medicine-statin interactions should be considered.[10] Medicines that inhibit liver enzymes may increase the concentration of the statin increasing the risk of skeletal muscle-related adverse effects such as myopathy or rhabdomyolysis.[9,10] Other medicines may increase the risk of muscle related adverse effects with statins through different mechanisms.[10]

Table 1: More commonly prescribed medicine-statin interactions amongst veterans based on the Australian Medicines Handbook (AMH) or Stockley's Drug Interactions*

Medicines to consider	Simvastatin	Atorvastatin	Fluvastatin	Pravastatin	Rosuvastatin
Amiodarone	✘	✘			
Verapamil	✘	✘			
Diltiazem	✘	✘			
Erythromycin	✘	✘		✘	
Clarithromycin	✘	✘		✘	
Fenofibrate	✘	✘	✘	✘	✘
Gemfibrozil	✘	✘	✘	✘	✘
Fluconazole	✘	✘	✘		
Itraconazole	✘	✘			
Ketoconazole	✘	✘			
Posaconazole	✘	✘			
Voriconazole	✘	✘			
Cyclosporin	✘	✘	✘	✘	✘
Imatinib	✘				
Sodium fusidate	✘	✘	✘	✘	✘

*Some of these interactions are based on case reports.

Note: Remember: if the statin is present in a combination product, it should also be considered.

The AMH and TGA websites provide further detailed information regarding medicine-statin interactions and specific actions to take.

There are other medicines that have the potential to interact with statins based on known pharmacological characteristics – for expert advice, contact a medicines information centre.

A word on oral anti-coagulants and statins[9]

If prescribing warfarin and statins, fluvastatin, rosuvastatin and simvastatin may increase the INR and subsequent risk of bleeding. Consider changing the statin to atorvastatin or pravastatin or decrease the warfarin dose according to the INR.

Caution should be exercised when prescribing dabigatran, rivaroxaban and apixaban with statins as the risk of bleeding may be increased.

Give careful consideration to patient characteristics and co-morbidities, the existing treatment regimen and the risk profile for medicine interactions when introducing any new medicine.[10] Use caution when introducing new medicines for older people as they often have the most co-morbidities, receive the greatest number of medicines and may be subject to age-related changes in organ function and pharmacokinetics making them the group most at risk for serious medicine-statin interactions.[19]

The clinical effects of an interaction may not be evident for some time after commencing a new medicine and may continue for some time after stopping a medicine-statin combination. Because patient response is often unpredictable and individual, not everyone will experience the same medicine-statin interaction and the severity of the interaction may differ from person to person.[9]

Consider a Home Medicines Review (HMR) if you are concerned about any potential medicine-statin interactions.

If interacting medicines that increase the risk of muscle related adverse effects are prescribed, consider:

- is your patient experiencing mild/moderate muscle-related adverse effects, (with or without a raised creatine kinase)?
  If so, is it appropriate to:
  - maintain the statin and choose a non-interacting medicine if possible
  - change the statin to a non-interacting statin if treatment is long-term
  - reduce the statin dose or potency
  - suspend the statin if new treatment is short-term (consider cardiovascular risk)
  - cease the statin permanently (consider anticipated clinical benefits against quality of life)
- reviewing your patient
- monitoring the clinical effect and creatine kinase as required
- encouraging your patient to report any unexplained muscle-related aches and pains, especially if accompanied by fever and malaise
- if acute clinical conditions that precipitate myopathy are observed, consider suspending statin temporarily[7,9]
- if a new medicine is commenced by a medical specialist and you have concerns, contact before continuing the combination.

Consider: When was the last clinical review undertaken?

Check alanine aminotransferase (ALT) and creatine kinase (CK) at the commencement of statin therapy and after dose adjustment until stable dose has been established. It is not recommended to routinely monitor ALT or CK thereafter unless symptoms of liver dysfunction or muscle-related adverse effects occur.[3]

Undertaking a clinical review of the patient may lead to a reassessment of statin therapy. If a patient has made substantial lifestyle changes and there has been an adequate reduction in individual risk factors, lowering the dose or reassessing the need to continue statin therapy may be a consideration. However, monitoring the patient for 12 months after is recommended to ensure changes are sustainable.[7]

When reviewing statin therapy, consider:

- the person's tolerance of statins and quality of life
- lowering the dose
- ceasing the statin.

Do statins increase the risk of developing diabetes, cancer or renal disease, and declining cognitive function?

There is a slight increased risk of developing new onset type 2 diabetes mellitus with statin therapy.[20,21] It is estimated one additional case of diabetes will result from treating 255 people with statins over four years while preventing 5.4 vascular events. Hence, recommendations are to continue statin therapy in patients with moderate or high cardiovascular risk or existing cardiovascular disease.[21,22]

There is no substantial evidence to support an increased risk of developing cancer or incurring cognitive decline due to statin therapy.[5,23]

There is recent evidence that statins may be linked to acute kidney injury. These results suggest careful consideration when prescribing high potency statins.[24]

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