FREQUENTLY ASKED QUESTIONS

FACT SHEET FOR GPs

SUMMARY HIGHLIGHTS

Atorvastatin has been selected for this pragmatic community based trial as it is the most commonly prescribed statin in Australia, has a favourable side effect profile and is one of the most potent statins in reducing LDL concentrations.

The Cholesterol Treatment Trialists' Collaboration (CTTC) meta-analyses published in September 2016, reported that a typical regimen, such as atorvastatin 40mg, taken for 5 years in 10,000 patients (age range 40-70 years) would on average prevent major cardiovascular events in 1000 patients for secondary prevention and 500 patients for primary prevention, with smaller proportions of patients experiencing adverse events; namely 5 cases of myopathy, 50-100 new cases of diabetes and 5-10 cases of haemorrhagic stroke.

STAREE will answer the clinically important question – "What is the balance between expected benefits versus harms for preventive treatment in people aged over 70 years?" There is currently a lack of evidence in this area to guide preventive statin therapy.

What do we know about statins for primary prevention in older adults?

Data from randomised controlled trials (RCTs) about the benefits and risks of statins for primary prevention for adults older than 70 years are limited, as relatively few older adults have participated in trials to date. PROSPER, the only study to specifically study statin use in older persons, combined both primary and secondary prevention populations. STAREE (Statins in Reducing Events in the Elderly) thus addresses a critical knowledge gap and aims to provide the evidence to support practice guidelines for primary prevention in a large community-based sample of people over 70 years of age.

STAREE aims to explore a full range of patient centred outcomes including health outcomes, quality of life, physical function, cognitive function and emotional well-being.

Why was atorvastatin chosen for the STAREE study?

- **Most commonly prescribed statin in Australia**
- **At low to standard dosing (20-40mg) it has a favourable side effect profile**
- **One of the most potent treatments in reducing LDL-C**

Atorvastatin is well researched with wide practice experience. Importantly, relative to other statins, it has a favourable side effect profile and has been shown to be one of the most potent statins for reducing low density lipoprotein concentrations (LDL-C) and triglyceride levels. It was chosen for these reasons and we expect that the dose of 40mg will produce around a 50% reduction in LDL-C and therefore significant reduction in CVD risk (see table next page).

	Daily dose of different statins				
	5 mg	10 mg	20 mg	40 mg	80 mg
Pravastatin	15%	20%	24%	29%	33%
Simvastatin	23%	27%	32%	37%	42%
Atorvastatin	31%	37%	43%	49%	55%
Rosuvastatin	38%	43%	48%	53%	58%

Shaded boxes indicate regimens that can produce about a halving or more in LDL cholesterol concentrations (largely irrespective of patient characteristics, including presenting concentrations of cholesterol). The 2016 cost for generic atorvastatin 40 mg daily in the UK is about £2 per 28 days of treatment;[184] rosuvastatin 20 mg daily currently costs about £25 per month,[185] but it became available as a generic in the USA during 2016.

Table: Average relative reduction in LDL cholesterol concentrations with different doses of commonly used statins (Collins, Reith et al. 2016).

Different statins have different potencies and newer therapies such as atorvastatin and rosuvastatin produce larger reductions in LDL-C per mg of drug than older therapies, such as simvastatin and pravastatin[1]. Adverse events associated with statin treatment may be more likely with higher doses of specific statins (i.e. simvastatin $\geqslant$ 80mg) and with combination therapy (i.e. statin and fibrate)[2,3].

A very important issue that has not been addressed is the balance between expected benefits and harms of statin therapy in people aged over 70 years. STAREE will provide evidence to address this.

See further information on specific adverse events below.

What is the risk for incident diabetes associated with statin therapy?

- **About 1% (100 cases in 10,000 treated) incident cases expected**
- **Most likely in patients with existing risk factors for type 2 diabetes**

Older people are at a high risk for the development of type 2 diabetes and the metabolic disturbances that precede it. The impact of statin therapy on incident risk has been reported across observational studies and several randomised control trials with varying effect estimates. Results from these studies vary depending upon factors such as statin type and dose, diabetes criteria, age of patients, range of biological predictors (i.e. fasting glucose, body mass) and whether they are primary or secondary prevention trials. In a 2010 meta-analysis of statin trials examining incident diabetes, statin use was associated with a 9% increased risk for incident diabetes with little heterogeneity between trials. Meta-regression indicated that the risk of developing diabetes was highest in trials with older participants [4]. In view of this data, in 2012 the FDA modified the labelling of statins to include a warning for the potential risk of increased blood sugar levels and new type 2 diabetes.

Since this meta-analysis, the JUPITER trial has examined diabetes risk in primary prevention [2]. The trial included 17, 802 patients, aged 60-72 years, randomised to either rosuvastatin 20mg daily versus placebo for 2-5 years and found the incidence of type 2 diabetes to be slightly higher in the treated group (3% versus 2.4% respectively, P = 0.01). Yet in those with diabetes risk factors, a total of 134 vascular events or deaths were avoided for every 54 new cases of diabetes diagnosed. For trial participants with no major diabetes risk factors, statin allocation was associated with a 52% reduction in major vascular events, a 53% reduction in venous thromboembolism, a 22% reduction in total mortality and no increase in diabetes.

Whilst the mechanism of statin related incident diabetes is not well understood, the relationship is likely to be dose-dependent and related to other diabetes risk factors. Based on the review by the CTTC, treatment of 10,000 people for 5 years with atorvastatin 40mg, would be expected to lead to 50-100 new cases of diabetes or ≤ 1% [1]. STAREE is in a unique position to add to this information by determining the risk to benefit ratio in a high risk group, namely individuals who are aged over 70 years.

Within STAREE, participants will be considered to have developed diabetes if HbA1c ⩾ 6.5% (48 mmol/mol) and Fasting Blood Glucose > 7.0mmol/L. Participants can enter the study with impaired fasting glucose if they have a normal Hba1c level. Once randomised to study treatment, participants who develop incident diabetes will be followed up on or off study medication; the latter if prescribed open label statin treatment.

How common are muscle symptoms? Who are at greatest risk?

- **Myalgia is commonly reported in older adults on statin therapy and also on placebo**
- **Myopathy is rare**
- **Statin-associated muscle symptoms (SAMS) are dose dependent, symmetrical and reversible**

Five statins (HMG CoA inhibitors) are available in Australia for the treatment of dyslipidaemia: simvastatin, atorvastatin, pravastatin, rosuvastatin and fluvastatin. Atorvastatin is the most commonly prescribed statin in Australia. All of the statins have been reported to cause myalgia and/or rhabdomyolysis. Cerivastatin was removed from the market worldwide because of an unacceptably high rate of rhabdomyolysis, including fatal cases, particularly when used with gemfibrozil (taken from the Australian Adverse Drug Reactions Bulletin, Volume 23, Number 1, February 2004; WHO Drug Information Vol. 18, No. 1, 2004).

All statins have been reported to cause muscle adverse events with the severity ranging from asymptomatic increases in creatinine kinase to myalgia (muscle aches, soreness, stiffness) to myopathy (muscle weakness and CK increase) to fatal rhabdomyolysis[5].

Myopathy is rare and the incidence of rhabdomyolysis is about 2-3 cases per 100, 000 treated patients[6]. The precise mechanisms causing statin induced muscle symptoms are not well-understood. Muscle symptoms are likely to be dose dependent, occur typically with 4 weeks of treatment but may occur even after therapy has been tolerated for up to 1 year, and are a leading reason for treatment withdrawal[1,3,7]. If statin induced, symptoms are likely to dissipate following cessation of therapy.

The estimated incidence of statin myopathy in trials has ranged from 1.4 to 5%, with a dose-dependent risk (higher risk with doses of statin > 40mg)[8]. Older age, female gender and concomitant use of inhibitors of cytochrome P450 3A4 are recognised risk factors for the development of statin myopathy[5,8,9].

Of the statins available in Australia, simvastatin is associated with the highest rates of myopathy at doses over 40mg. Simvastatin and atorvastatin are both metabolised by CYP3A4 pathway and are more likely to be associated with myopathy when patients are also taking drugs that inhibit this pathway (taken from the Australian Adverse Drug Reactions Bulletin, Volume 23, Number 1, February 2004; WHO Drug Information Vol. 18, No. 1, 2004).

In a meta-analysis of 26 masked RCTs (including the STOMP trial; specifically designed to assess the effects of statin therapy, atorvastatin 80mg versus placebo) myalgia was common (in middle to older aged adults, 50-70 years) with comparable rates in treated (12.7%) and untreated participants (12.4%)[3].

Statin-associated muscle symptoms are likely to be symmetrical, affect large muscle groups and disappear when treatment is ceased. In STAREE, participants who report muscle adverse effects may be offered a treatment rechallenge at a lower dose.

<u>Management of statin associated muscle symptoms:</u>

If patients complain of muscle symptoms, the EAS Society Consensus Panel recommends that clinicians should:

- *Evaluate risk factors that may pre-dispose to SAMS (female gender, ethnicity, multisystem disease and small body frame)*
- *Exclude secondary causes (e.g. hypothyroidism)*
- *Review other medications that may cause muscle related side effects*
- *Review drug-drug interactions that may increase the risk of SAMS*

Managing patients who are identified with elevated creatine kinase (CK)

- **The incidence of elevated CK levels in patients treated with statin therapy is uncertain.**
- **Myalgia is a common side effect of statin therapy (occurring in 1-5%) and is sometimes associated with a rise in CK level.**
- **Myopathy and rhabdomyolysis occur rarely (< 0.1%) and are associated with a more marked elevation of CK level. The risks of myopathy and rhabdomyolysis are dose related and increased by illness and drug interactions.**
- **A number of factors impact upon CK levels so the specificity of this result, pertaining to statin myopathy, is low. It is recommended that all likely causes for elevated CK levels are investigated.**

The Product Information and TGA guidance on statin use does not recommend routine monitoring of CK for all patients commencing statin. Rather periodic creatine kinase (CK) levels can be checked as clinically indicated. However there is no assurance that monitoring will prevent the occurrence of myopathy.

The Australian Medicines Handbook (AMH) recommends during statin therapy to "stop statin if CK concentration is > 10 times upper limit of normal, or if there is persistent unexplained muscle pain (even if CK is normal).[10]

Suitability for recommencement of the statin medication can be determined by you, the treating doctor after appropriate follow-up pathology tests and review of the patient's clinical situation.

Managing patients who are identified with elevated transaminases (AST & ALT)

- **The incidence of true liver injury caused by statin therapy is low**
- **In statin-treated patients, an increase in liver enzymes may be due to different aetiologies, which should be considered before assuming the increase in liver enzymes is due to the statin.**

It is recognised that one third of the population will have asymptomatic elevations in liver function tests (LFTs) at any time[11]. Many pre-existing conditions can cause elevations in transaminase levels (e.g., chronic viral hepatitis, nonalcoholic fatty liver disease) and these were once thought to be contraindications to statin therapy; however, statins do not worsen liver function in most patients with chronic liver disease[12].

Mild to modest increases in liver enzymes (i.e. ALT 70-80 IU/L) are not necessarily a contraindication to either initiation or continued use of statins, especially if the clinical presentation and subsequent assessment suggests non-alcoholic fatty liver disease as the reason for the liver enzyme elevation [13].

Persistent and substantial (i.e. > 180 IU/L) ALT elevations and /or AST elevations in the presence of elevated bilirubin levels (i.e. total > 3.8 mg/dL) without elevated alkaline phosphatase is likely to indicate significant liver injury (Hy's law criteria)[13]. Statin associated liver toxicity is rare.

*In STAREE, AST and ALT levels are tested annually. A notification letter will be sent to the treating GP if an abnormality is detected, namely if the levels are 3 times the upper limit of normal (i.e. Melbourne Path: AST > 90 IU/L and ALT > 105 IU/L). It is recommended these people are followed up with their GP for clinical assessment and repeat liver function (*complete panel including Total Protein, Albumin, ALT, AST, ALP, GGT and Bilirubin) *testing in 4 weeks.*

<u>Liver task force recommendations</u>:

- *ALT and AST > 3xULN – repeat ALT and AST as soon as possible to determine if the abnormality is persisting*
- *If elevation has persisted, cease statin therapy until greater diagnostic clarity is obtained*
- *Perform blood testing to better assess liver function and evaluate potential causes of liver toxicity*

Statin treatment in patients with low baseline LDL levels – are there clinical concerns?

- **No adverse events reported to date with LDL-C lowering to 1.4 mmol/L**

The Cholesterol Treatment Trialist Collaborations (CTTC) review published recently indicated that the degree of LDL reduction is influenced by baseline LDL level, absolute risk for a major cardiovascular event and adherence to therapy (with greater efficacy following 1+ year on treatment)[1]. A typical dose of 40mg atorvastatin is expected to reduce LDL-C by about 50%, for example from 2 mmol/L to 1 mmol/L (77.3 to 46.4 mg/dL). However the proportional risk reduction with such LDL-C reduction for individuals over the age of 75 years is not known.

The JUPITER trial, a primary prevention trial that included participants who had baseline LDL cholesterol concentrations less than 3.37 mmol/L and randomised to 20mg rosuvastatin or placebo, showed that by 12 months, the treated group experienced 50% reduction in LDL level (triglycerides level reduced by 17% and no change to HDL levels)[14]. In this study, the median treated LDL level was 1.2 mmol/L (46.4 mg/dL). In those with LDL concentrations less than 1.2 mmol/L, the side effects of treatment were similar to those with LDL concentrations greater than 1.2 mmol/L[2].

No RCT has targeted specific LDL-C levels however the IMPROVE-IT trial did report a significant proportion of participants achieving low LDL-C levels[15]. The IMPROVE-IT trial, a secondary prevention trial for acute coronary syndrome, examined event rates in 18,144 patients treated with simvastatin 40mg + placebo or simvastatin 40mg + ezetimibe 10mg for a median of 6 years. The LDL-C was 1.8 mmol /L in the former and 1.4 mmol/L in the latter group. Whilst the rates of major cardiovascular events was significantly lower in the simvastatin + ezetimibe group, no significant between-group differences were seen in the percentage of patients who had elevations in alanine aminotransferase levels that exceeded three times the upper limit of the normal range or in the rates of gallbladder-related adverse events, cholecystectomy, muscle-related adverse events, or new, relapsing, or worsening cancer, or the rates of haemorrhagic stroke (although the number of cases was low). It was concluded that achieving low LDL-C levels did not produce any significant safety concerns[15]. Of note, this trial had a lipid monitoring committee in conjunction with a data safety monitoring board.

Do statins cause memory loss or changes in cognitive performance in older people?

Whether statins are beneficial, harmful or have no effect on cognition in older people with normal cognition or impaired cognition is unknown.

While memory and/or cognitive changes are frequently reported by patients taking statin therapy, on balance, the current available literature, which is limited, does not suggest that statins have adverse effects on cognition.

Despite this, the Federal Drug Administration of the United States currently requires a label warning to indicate that statins may be associated with cognitive effects – this is based on information from its passive surveillance adverse event reporting system (AERS).

- The statin effects on memory reported through AERS were usually not serious and reversed when patients stopped taking the drug
- Time to onset of impairment was highly variable, ranging from 1 day to years after first statin exposure
- There were no associations between cognitive impairment and specific statins or statin doses, specific age groups or concomitant medication use.

In addition to spontaneous case reports, data is available from longitudinal cohort studies and a small number of randomised controlled trials. Cohort studies show either no effect or a beneficial effect of statins and memory in the elderly, while RCTs show no effect. However, most of these published studies have numerous limitations, including:

- short duration of follow-up
- not accounting for other risk factors for cognitive decline
- not accounting for baseline cognitive performance
- lack of rigorous and detailed assessment of memory and cognition

- low representation of older people

Overall, considering all available studies that have been conducted in older populations, and their limitations, there is moderate evidence that statins:

- do not increase the risk of dementia in the elderly
- do not increase the risk for mild cognitive impairment in the elderly
- do not worsen global cognitive performance in the cognitively intact or impaired
- do not worsen memory function in the elderly

There is low strength evidence that statins do not increase the risk of Alzheimer's disease.[16]

Clinicians should be open to patient complaints of cognitive or memory change.

Recommendations:

- *If a cognitive deficit is found it is important to screen for other causes (e.g. hypothyroidism, vitamin B12 deficiency, depression) and actively screen for and treat cerebrovascular risk factors such as hypertension and diabetes.*
- *Appropriate referral for formal neurocognitive examination, screening and if indicated, treatment, may be required*

Useful links

The uncertainty of primary prevention in those over 75 : http://jamastatins.com/

NICE guidelines; recommend Atorvastatin (20mg) as primary prevention therapy in older persons with a 10% risk of a CVD event or risk of CVD across 10 years : https://www.nice.org.uk/guidance

WHO drug information: WHO statin drug information 2004

TGA : https://www.tga.gov.au/alert/statins

AMH Online (members only): AMH drug reference

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