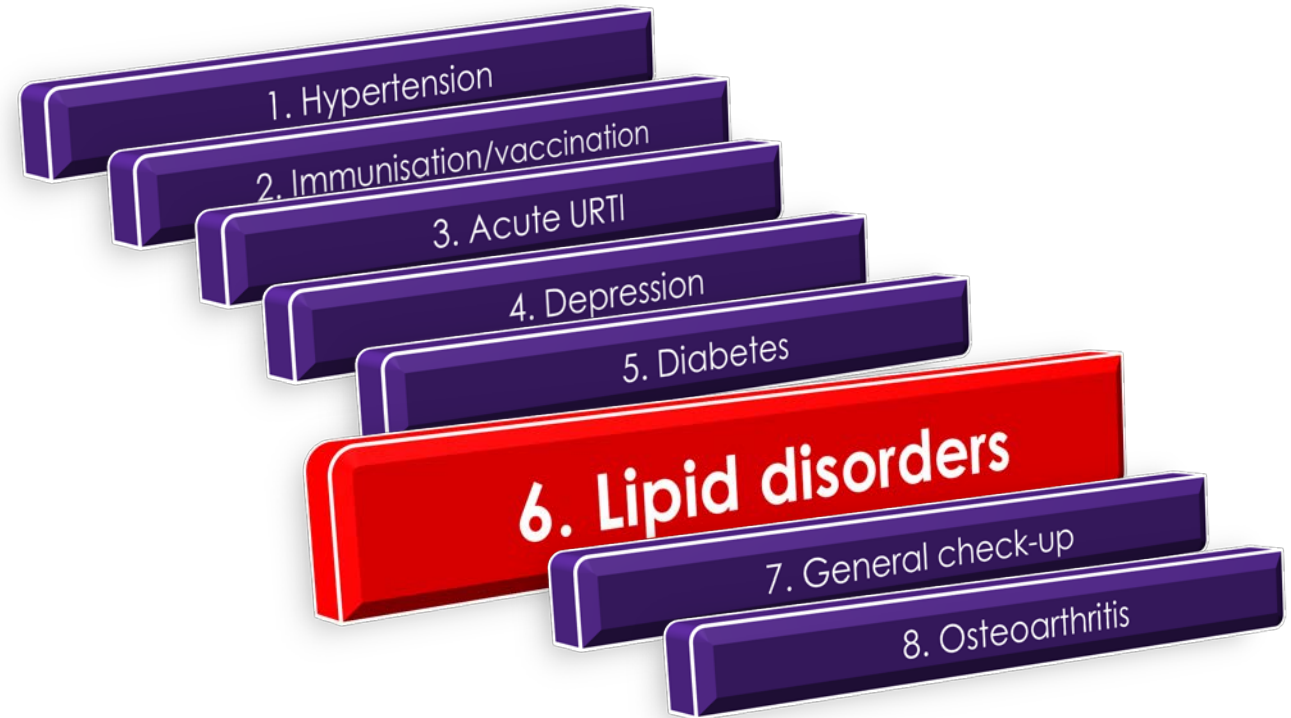
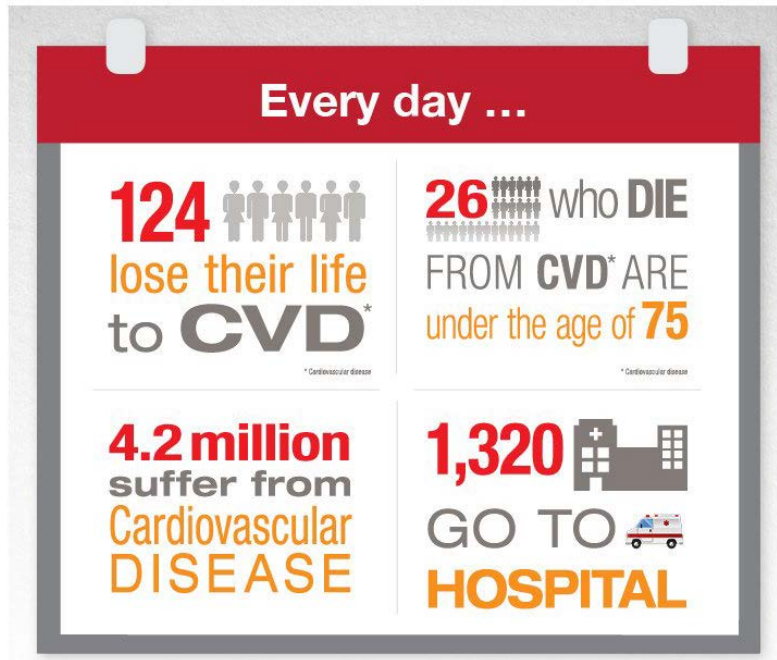


# STATINS: OPTIMISING THERAPY, ADDRESSING INTOLERANCE

Natalie Raffoul B.Pharm (Hons), GradCertPharmMed, MPS

Joanne Gross B.Pharm (Hons), MPH, GradCertPharmPrac, BCGP, MSHPA

# Cardiovascular disease



Most frequently managed conditions in Australian general practice

# 5 Reasons Why You SHOULD NOT Take Statins



© iStock.com / rogerashford

# ALERT! STATINS May NOT Be EFFECTIVE or SAFE



© iStock.com / rogerashford

## STATINS DO HARM.

*You are better off  
without them!*

Alternative-Doctor.com  
Dr. Keith Scott-Mumby

## Muscle Damage

Cholesterol Drug

## The DANGERS of STATIN DRUGS



© SenNovik / iStock / Thinkstock

### CASE SCENARIO

#### Meet Jim

Jim, a 52-year-old man who recently moved into the area, presents at your practice for the first time.

His primary reason for the visit is to have a flu vaccination, because he had a very bad episode of the flu last year, and he was on annual leave when the vaccination was offered at his workplace.

He also says he is currently taking lisinartan 10 mg daily, after being diagnosed with high blood pressure 6 years ago, and needs a new script. In addition, because it's been a while since he had his cholesterol and glucose checked, he asks if he should have that done as well.

Jim gives his medical history. He agrees to come back for a visit to discuss the results and your recommendations.

#### Medical history

Hypertension, diagnosed 6 years ago. Annual heartburn.

#### Family history

Father had a stroke at age 54. Died at age 74.  
Mother had type 2 diabetes. Died at age 82.

#### Allergies

Nil known.

#### Current medicines list

Medicine	Dose
Lisinartan	10 mg daily
Hydralazine	50 mg

#### Blood test results (non-fasting)

Result	Target
TC	< 4.0 mmol/L
HDL-C	> 1.0 mmol/L
LDL-C	< 2.0 mmol/L
TG	Normal range
Blood glucose	< 5.5 mmol/L
HbA <sub>1c</sub>	< 6.5%

#### Examination

BP	130/90 mmHg
WT	82 kg
Visual examination	Normal
Visual examination	Normal

### MEDICINEINSIGHT

#### Statin: optimising therapy, addressing intolerance

The following information is an extract from the MedicineInsight report 'Statin: optimising therapy, addressing intolerance'.

**What proportion of patients with high CV risk are being treated with statins?**

**For patients on statin therapy, what was their CV risk before starting treatment?**

### MedicineInsight report visit

#### Lipid management

Dyslipidaemia is commonly managed in general practice and is a major risk factor for cardiovascular (CV) disease.

Lipid-modifying medicines in combination with lifestyle interventions are recommended to achieve target lipid levels in those with high CV risk.

Lipid levels should be re-assessed in the context of cardiovascular risk when making decisions about management.

#### Who are your patients?

Category	Your practice	All practices
All regular patients in your practice	5000	35.0
Age 45-74 years	1823	8.1
with dyslipidaemia	427	7.8
with hypertension (total)	394	4.0
on statins	445	8.8
on statins with high CV risk*	420	8.3
All Aboriginal and Torres Strait Islander patients in your practice	20	0.6
with high CV risk*	20	0.6

#### Age and sex profile of regular patients in your practice with dyslipidaemia

### Statin: optimising therapy, addressing intolerance

#### What would you do if a patient on statin therapy presented with muscle symptoms?

#### SAMS Assessment Guide

**SAMS MORE LIKELY**

**Nature of symptoms\***

- Large muscle groups (eg thighs, buttocks, calves, shoulder girdle)
- Muscle aches, weakness, soreness, aches, cramping, tenderness or general fatigue

**Timing of symptoms\***

- Onset 4-6 weeks after statin initiation
- Onset after statin dosage increase

**Other considerations\***

- Risk factors for SAMS including:
  - moderate or fast albuminuria
  - high-dose statin therapy
  - history of myopathy with other lipid-modifying medicines
  - regular vigorous physical activity
  - impaired hepatic or renal function
  - substance abuse (eg alcohol, cocaine, cannabis, heroin)
  - low BMI
- Elevated CK levels

**CK levels\***

- Elevated (> 10x ULN, but may also be normal)
- Elevated CK levels decrease after statin is discontinued

### Statin: optimising therapy, addressing intolerance

#### Pharmacy visit

#### Case study

Consider the online case study in your resources. Include advice on your response when receiving this information when receiving this information.

#### Pharmacy Practice Review: Statins: promoting adherence, addressing intolerance

Participate in the Pharmacy Practice Review and learn to recognise barriers to statin adherence. Improve adherence to statin therapy. Share your findings with your colleagues. Review if you support SAMS. Share your knowledge on statin dose CV risk.

#### Tool SAMS assessment guide and management algorithm

Note: Algorithm offers GPs guidance on the systematic management of patients with suspected statin-associated muscle symptoms (SAMS). This tool is provided for interested practitioners to use.

#### Patient Information Sheet: FAQs

Evidence-based information to answer some of the common questions asked by patients who are prescribed statins to reduce cardiovascular risk.

#### MedicineWise app

Our popular MedicineWise app has recently been upgraded with a new theme, features and functionality. The app includes the SAMS assessment guide and management algorithm, patient information sheets, and more. It's available for free download on the App Store and Google Play.

# Multifaceted national educational visiting program targeting young GPs

### MEDICINEWISE NEWS

#### UNCOVERING THE TRUTH ABOUT STATIN INTOLERANCE

**Key points:**

- Muscle symptoms are the most commonly reported form of statin intolerance.
- The true incidence of statin-associated muscle symptoms is likely to be lower than what is observed in clinical practice.
- There is no standardised definition or diagnostic test for statin-associated muscle symptoms.
- Systematic assessment of muscle complaints can help healthcare professionals establish whether statin intolerance is the likely cause, and manage patients accordingly.

#### Statin: optimising therapy, addressing intolerance

Statin intolerance is an inability to tolerate the dose of a statin (umbrella term).

Statin intolerance is an inability to tolerate the dose of a statin (umbrella term).

Statin intolerance is an inability to tolerate the dose of a statin (umbrella term).

### FACTSHEET

#### STATIN MEDICINES

#### Frequently asked questions

##### Statin: optimising therapy, addressing intolerance

Statins are medicines that work to lower the level of LDL cholesterol (commonly known as bad cholesterol) in your blood. They also help to reduce the chance of having a heart attack or stroke for people who are at high risk.

##### What can a statin help?

If you have had a heart attack or stroke, your risk of having another similar event within the next 5 years is high. Taking a statin can substantially lower that risk - on average by around 20%.

##### What about side effects?

All medicines (prescription or over-the-counter) can have side effects, even when taken for the same condition.

##### Who should be prescribed a statin?

Australian guidelines recommend health professionals prescribe a statin according to (a) a heart attack or stroke in the next 5 years, (b) a low-density lipoprotein cholesterol (LDL-C) level of 5 mmol/L or above, (c) a family history of cardiovascular disease.

### Educational visits

### Online Case Study

#### CASE STUDY

##### Optimising statin therapy

How do we optimise a patient's statin therapy for the management of dyslipidaemia with minimal side effects?

### Pharmacy Practice Review

### nps.org.au/statins

### Clinical e-Audit

### MedicineWise News

### Statins FAQ

# CASE STUDY

# Meet Jim

- ▶ 52-year-old man who recently moved into the area
- ▶ Presents at your practice for the first time for a flu vaccination.
- ▶ It's been a while since he had his BP, cholesterol and glucose checked



# Meet Jim

## Medical history

Hypertension, diagnosed 6 years ago.  
Occasional heartburn.

## Family history

Father had a stroke at age 54. Died at age 74.  
Mother had type 2 diabetes. Died at age 82.

## Allergies

Nil known.

## Social history

Lives with wife and two boys (15 & 18yo)  
Graphic designer

## SNAP

Lunches are often deep-fried takeaway  
Jim has been a smoker for 20 years, smoking 20 cigarettes per day.  
He has tried to quit smoking a number of times; all attempts have been unsuccessful.  
He has about 2-3 beers per week.  
Sedentary

## Current medicines list

MEDICINE	DOSE
Irbesartan	150 mg daily
Mylanta	prn

# Meet Jim

## Blood test results (non-fasting)

### Lipid profile

TC	6.4 mmol/L	<b>Target</b>	< 4.0 mmol/L
HDL-C	0.8 mmol/L		≥ 1.0 mmol/L
LDL-C	4.5 mmol/L		< 2.0 mmol/L
TG	2.4 mmol/L		< 2.0 mmol/L

### Blood glucose

Blood glucose	5.0 mmol/L	<b>Normal range</b>	< 5.5 mmol/L
HbA <sub>1c</sub>	43.2 mmol/mol 6.1%		< 48 mmol/mol < 6.5%

## Examination

### BP

136/86 mmHg

### BMI

32 kg/m<sup>2</sup>

### Waist circumference

108 cm



# Small group discussion

WHAT ARE THE  
MANAGEMENT  
**ISSUES** FOR JIM?

## Consider...

His lipid profile

What CV risk factors does he have?

Further screening

WHAT IS YOUR  
MANAGEMENT  
**PLAN** FOR JIM?

## Consider...

- ▶ How will you quantify his risk
- ▶ How will you manage his risk?
- ▶ What do you need to check at baseline?
- ▶ Ongoing monitoring

*Considering Jim's lipid profile,  
what would you do?*



**Blood test results (non-fasting)**

**Lipid profile**

TC 6.4 mmol/L  
HDL-C 0.8 mmol/L  
LDL-C 4.5 mmol/L  
TG 2.4 mmol/L

**Target**

< 4.0 mmol/L  
≥ 1.0 mmol/L  
< 2.0 mmol/L  
< 2.0 mmol/L

**Blood glucose**

Blood glucose 5.0 mmol/L  
HbA<sub>1c</sub> 43.2 mmol/mol  
6.1%

**Normal range**



< 5.5 mmol/L  
< 48 mmol/mol  
< 6.5%

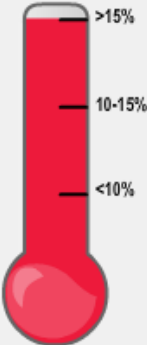
# Jim's absolute risk profile

## Australian absolute cardiovascular disease risk calculator

Enter patient information below:

PRINT

Sex	<input checked="" type="radio"/> Male	<input type="radio"/> Female
Age	<input type="text" value="52"/>	years
Systolic blood pressure	<input type="text" value="136"/>	mmHg
Smoking status	<input checked="" type="radio"/> Yes	<input type="radio"/> No 
Total cholesterol	<input type="text" value="6.4"/>	mmol/L
HDL cholesterol	<input type="text" value="0.8"/>	mmol/L
Diabetes	<input type="radio"/> Yes	<input checked="" type="radio"/> No 
ECG LVH	<input type="radio"/> Yes	<input type="radio"/> No <input checked="" type="radio"/> Unknown



Your heart and stroke risk score is **17%**  
This means you are at high risk of getting cardiovascular disease in the next 5 years.  
[Click here](#) if you would like to have a look at the information on this website that explains what your risk score means.  
The next step is to talk to your doctor about what steps you can take to lower your chance of getting cardiovascular disease.  
Please note: the absolute risk calculator score is only a guide to your heart and stroke risk score. Print out this page and take it to your doctor for further information on your personal risk.  
[View guidelines and resources](#)



An initiative of the National Vascular Disease Prevention Alliance

16:44 - Monday 21/08/2017

# Guidelines recommend...

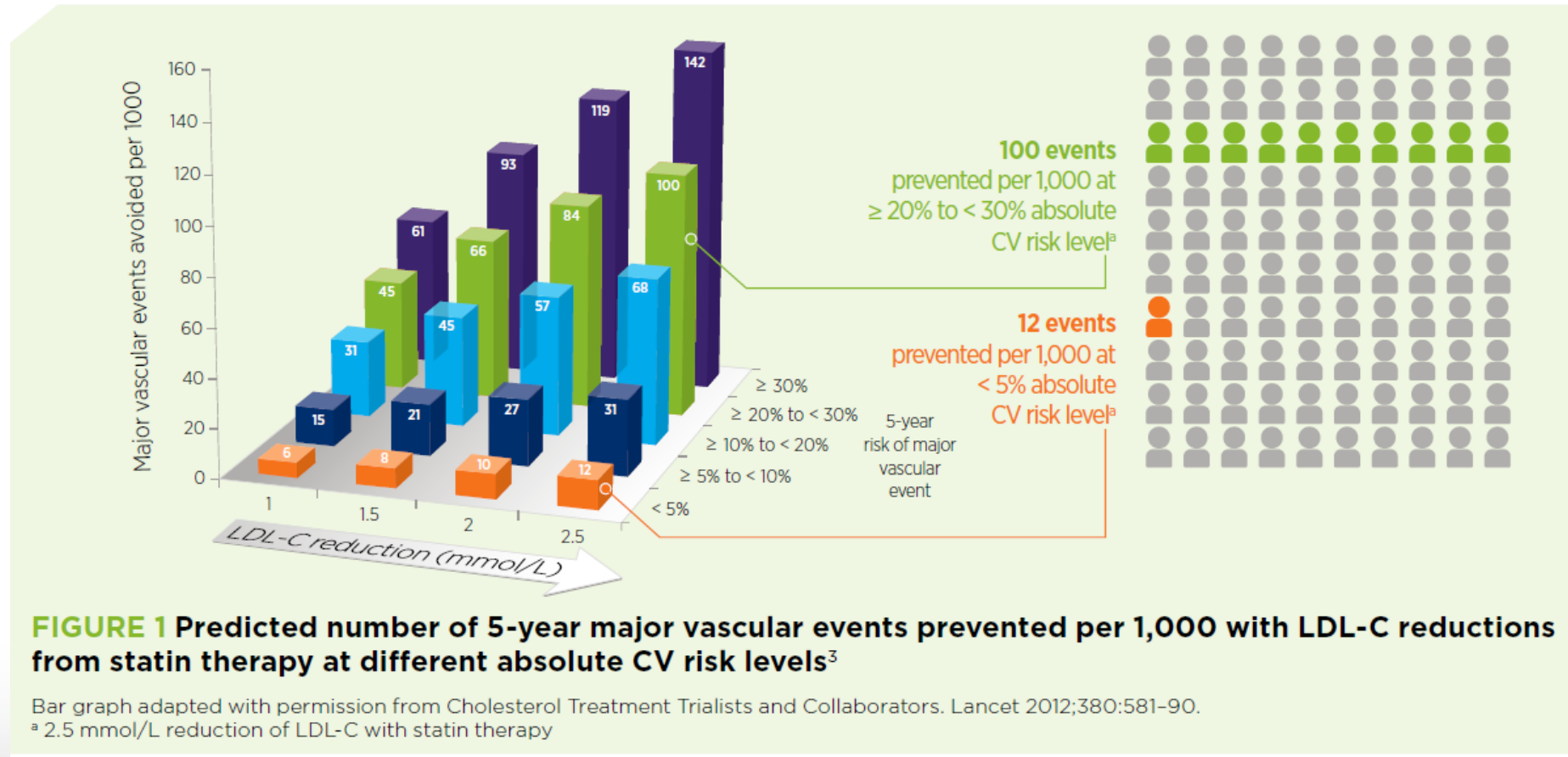
- **High absolute CV risk or established CVD**
  - Prescribe lipid-modifying medicines with lifestyle modification
- **Moderate absolute CV risk**
  - Try lifestyle modification before considering lipid-modifying medicines
- **Low absolute CV risk**
  - Encourage lifestyle modification; recognise that lipid-modifying medicines are usually not required



**Choosing Wisely**  
Australia

*Don't commence therapy for hypertension or hyperlipidaemia without first assessing the absolute risk of a cardiovascular event.*

# Why treat high risk patients?



# High risk patients missing out on statins

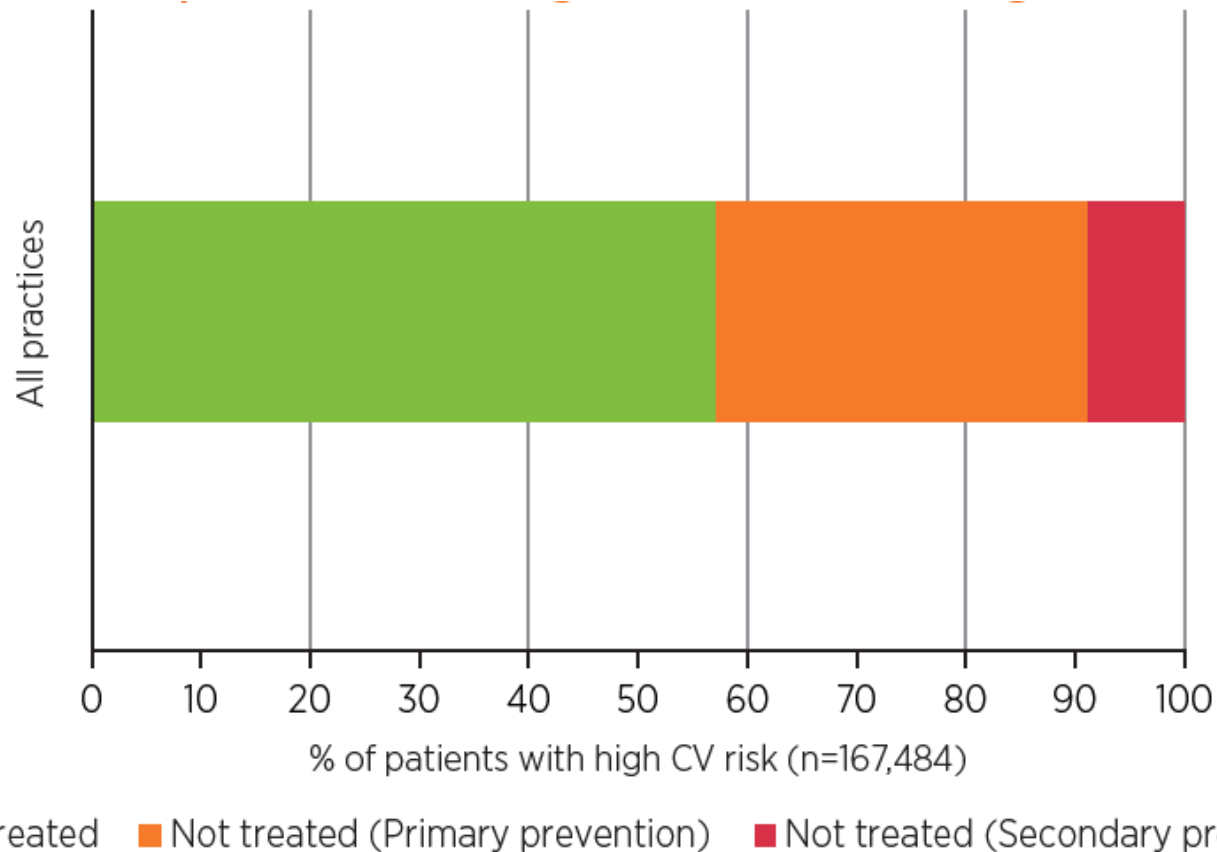


Figure 1: Proportion of patients aged 45-74 years at high CV risk according to statin treatment and prevention status

Now consider Jim with the same lipid profile, but no history of elevated BP or smoking.

Would you recommend a lipid-modifying medicine?

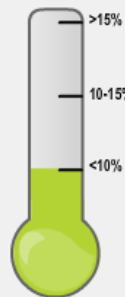


## Australian absolute cardiovascular disease risk calculator

Enter patient information below:

PRINT

Sex  Male  Female  
Age  years  
Systolic blood pressure  mmHg  
Smoking status  Yes  No   
Total cholesterol  mmol/L  
HDL cholesterol  mmol/L  
Diabetes  Yes  No   
ECG LVH  Yes  No  Unknown



Your heart and stroke risk score is  
**7%**

This means you are at low risk of getting cardiovascular disease in the next 5 years.

[Click here](#) if you would like to have a look at the information on this website that explains what your risk score means.

The next step is to talk to your doctor about what steps you can take to make sure you stay at low risk for getting cardiovascular disease.

Please note: the absolute risk calculator score is only a guide to your heart and stroke risk score. Print out this page and take it to your doctor for further information on your personal risk.

[View guidelines and resources](#)



strokefoundation

### Blood test results (non-fasting)

#### Lipid profile

TC	6.4 mmol/L
HDL-C	0.8 mmol/L
LDL-C	4.5 mmol/L
TG	2.4 mmol/L

#### Blood glucose

Blood glucose	5.0 mmol/L
HbA <sub>1c</sub>	43.2 mmol/mol 6.1%

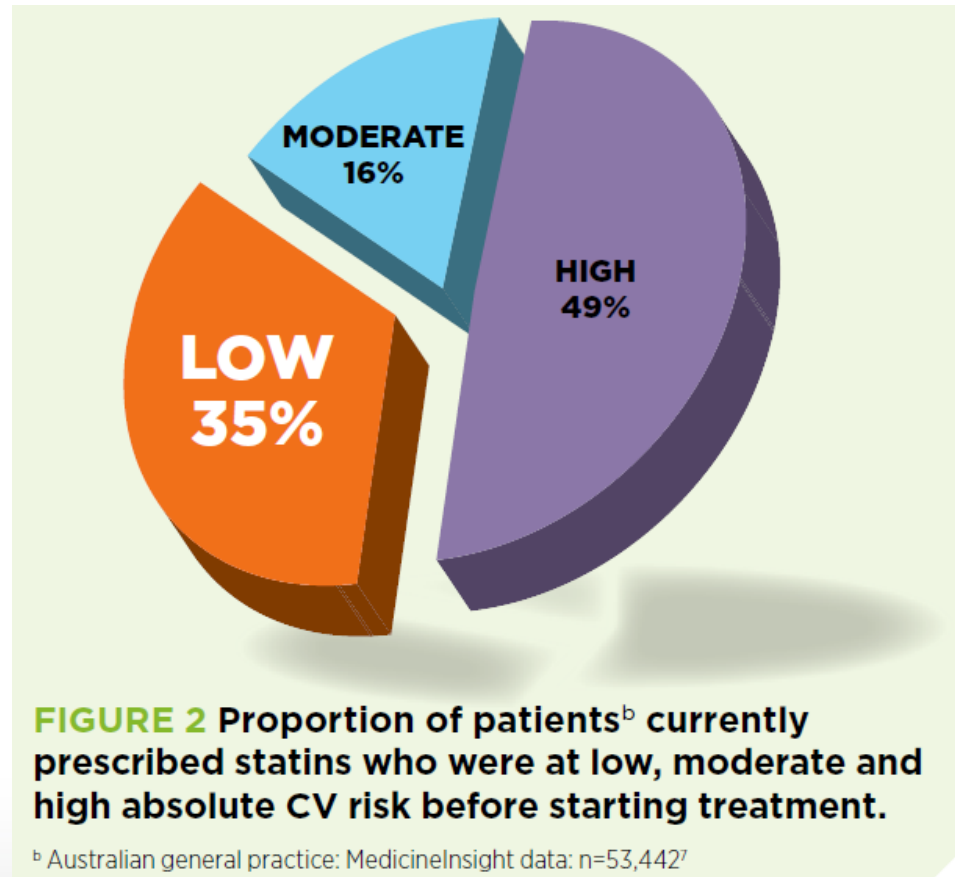
#### Target

< 4.0 mmol/L
≥ 1.0 mmol/L
< 2.0 mmol/L
< 2.0 mmol/L

#### Normal range

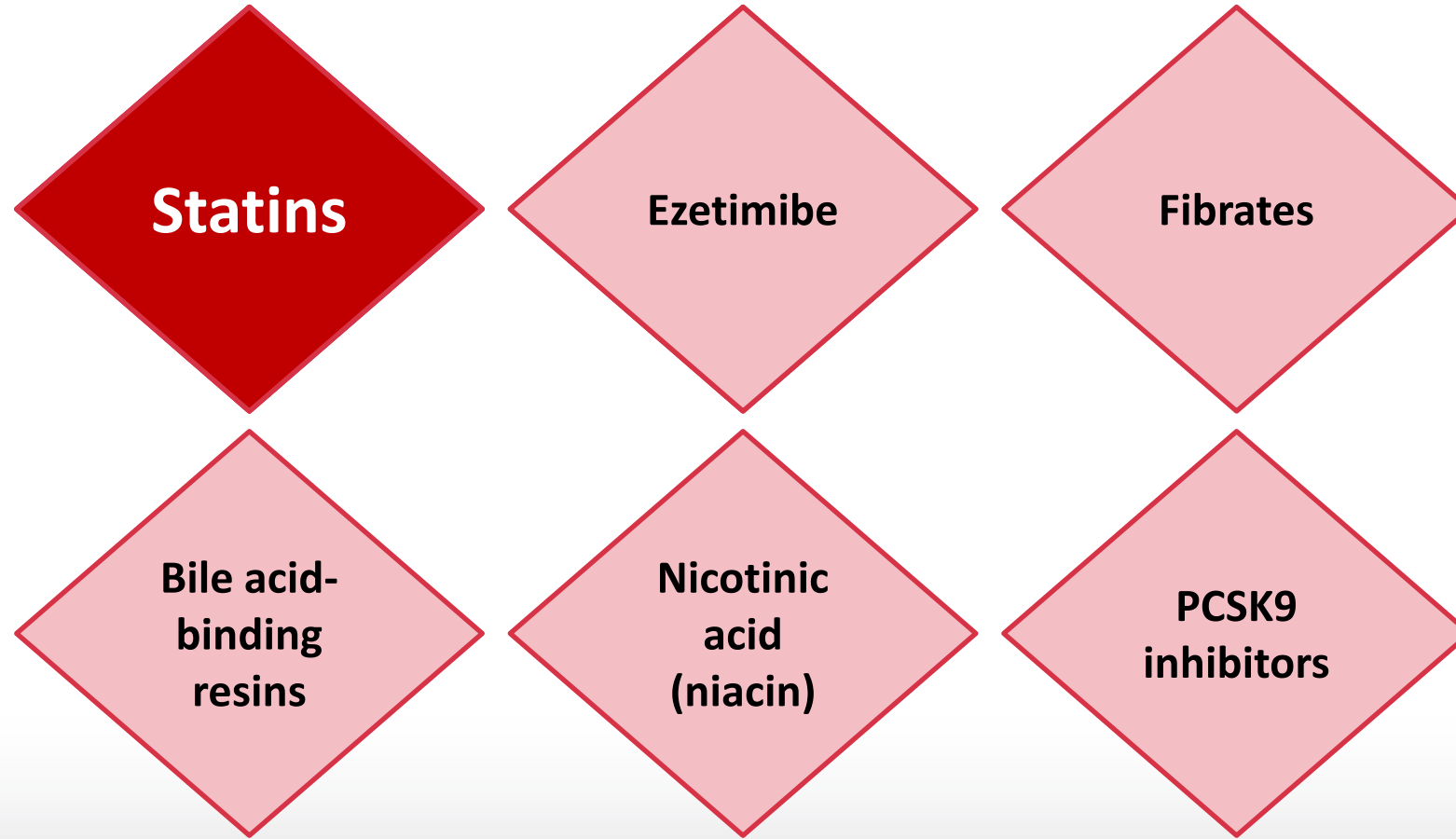
< 5.5 mmol/L
< 48 mmol/mol < 6.5%

# Overprescribing of statins?





# Which lipid-modifying therapy to prescribe?



# Statins are still first line

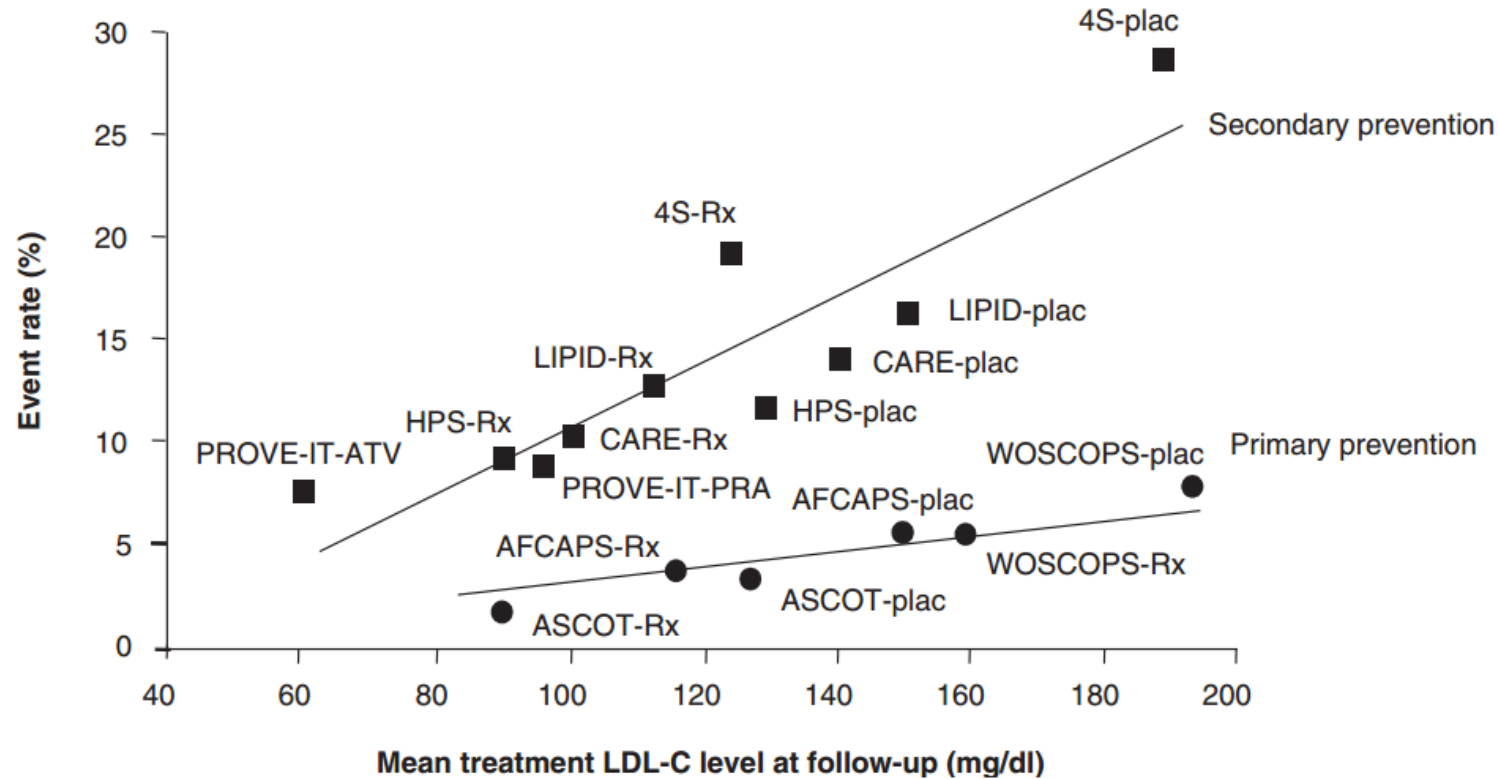


## Statins

### Risk reduction per 1 mmol/L decrease in LDL-C

All-cause mortality	12%
CHD death	19%
Major coronary events	23%
Coronary revascularisation	24%
Ischaemic stroke	19%
Major vascular events	21%

# LDL-C: 'the lower the better'?



**Figure 1.** Relationship between on-treatment LDL-C and cardiovascular events in landmark statin trials.

# The longer the duration, the better?

**Table 2:** Expected proportional risk reduction based on pre-treatment LDL-C, absolute magnitude of LDL-C reduction, and total duration of therapy.

Baseline LDL-C (mmol/L)	Absolute reduction LDL-C (mmol/L)	Duration of treatment exposure [expected proportional risk reduction (%)]				
		5 years	10 years	20 years	30 years	40 years
7	3.5	58	68	81	89	93
7	3.0	53	62	76	85	90
7	2.5	46	56	70	79	86
7	2.0	39	48	61	71	79
7	1.5	31	39	51	61	69
5	2.5	46	56	70	79	86
5	2.0	39	48	61	71	79
5	1.5	31	39	51	61	69
5	1.0	22	28	38	46	54
3	1.5	31	39	51	61	69
3	1.0	22	28	38	46	54
3	0.5	12	15	21	27	32
2	1.0	22	28	38	46	54
2	0.5	12	15	21	27	32

# Which statin?



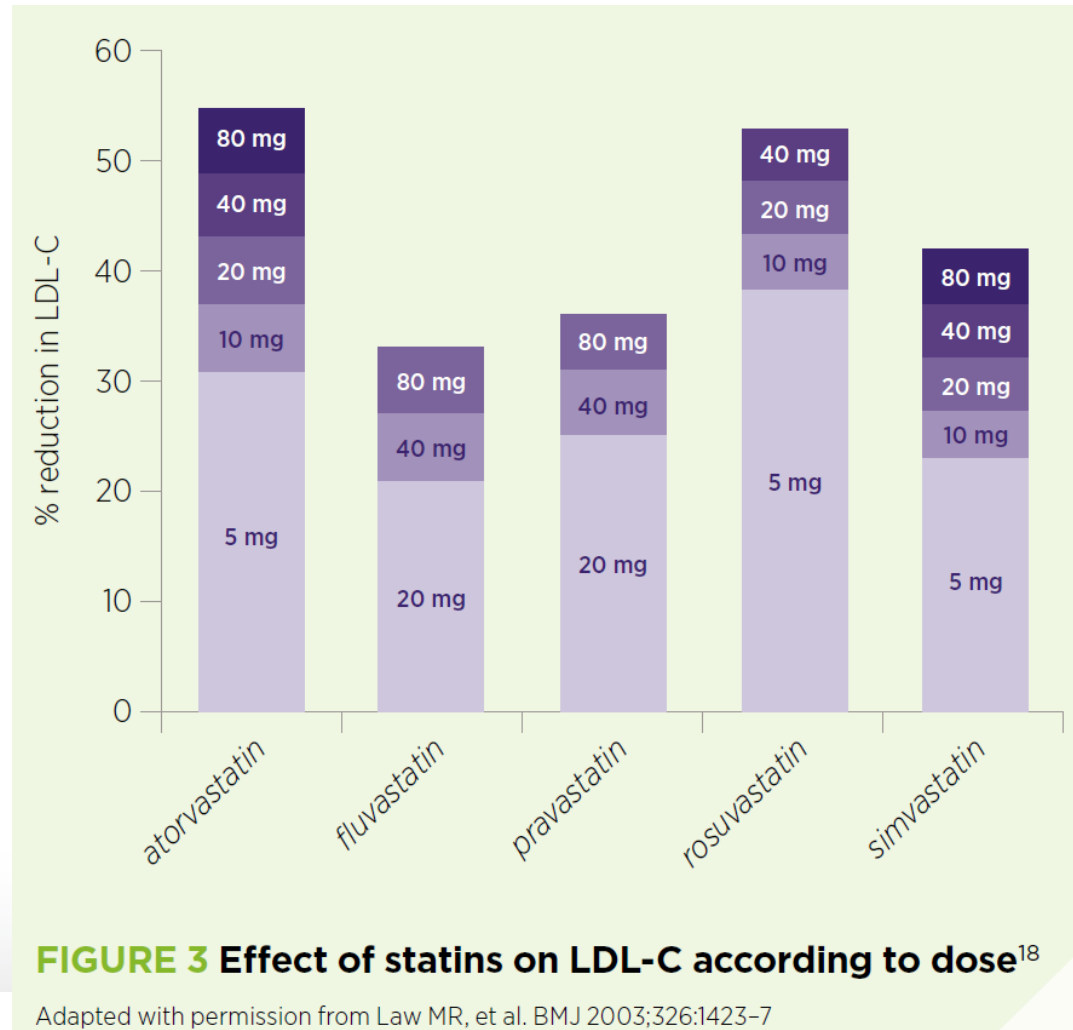
# BUT first, what are you aiming for?



## Australian guideline recommended lipid targets

TC	< 4.0 mmol/L
HDL-C	≥ 1.0 mmol/L
LDL-C	< 2.0 mmol/L primary prevention
	< 1.8 mmol/L secondary prevention <sup>c</sup>
Non-HDL-C	< 2.5 mmol/L
TG	< 2.0 mmol/L

# Dose equivalency



# Drug interactions (CYP450)

TABLE 1

Examples of cytochrome P450-mediated statin medicine interactions<sup>17</sup>

STATIN	METABOLISED BY	STATIN CONCENTRATION MAY BE INCREASED BY	STATIN CONCENTRATION MAY BE DECREASED BY
<b>Atorvastatin</b> <b>Simvastatin</b>	CYP3A4 (main)	CYP3A4 inhibitors <ul style="list-style-type: none"> <li>● Azole antifungals (all)</li> <li>● Calcium channel blockers (only diltiazem, verapamil)</li> <li>● Fluvoxamine</li> <li>● Grapefruit juice</li> <li>● HIV-protease inhibitor antiretrovirals (all)</li> <li>● Macrolide antibacterials (only clarithromycin, erythromycin)</li> <li>● Ticagrelor</li> </ul>	CYP3A4 inducers <ul style="list-style-type: none"> <li>● Antiepileptics (some eg, carbamazepine, phenytoin)</li> <li>● HIV-protease inhibitor antiretrovirals (only ritonavir, tipranavir)</li> <li>● Rifampicin</li> <li>● St John's wort</li> </ul>
<b>Fluvastatin</b>	CYP2C9 (main) CYP3A4 (lesser extent)	CYP2C9 inhibitors <ul style="list-style-type: none"> <li>● Amiodarone</li> <li>● Azole antifungals (only fluconazole, voriconazole)</li> <li>● SSRIs (only fluoxetine, fluvoxamine)</li> </ul> CYP3A4 inhibitors (see above)	CYP2C9 inducers <ul style="list-style-type: none"> <li>● Rifampicin</li> <li>● St John's wort</li> </ul> CYP3A4 inducers (see above)
<b>Pravastatin</b> <b>Rosuvastatin</b>	Not significantly metabolised by CYP enzymes		



# Statin initiation and monitoring

## START STATIN

At baseline check:

- CK
- ALT
- BSL

Counsel patients about what to expect when taking statins

## CHECK AT 4 –8 WEEKS

- Lipids
- Adherence
- Lifestyle
- Adverse effects

*Non-fasting* lipid samples recommended in most cases

Non-adherence rates up to 67% after 12 months

Ongoing routine CK or ALT tests not recommended

# So, back to Jim...

He agrees to start atorvastatin 20 mg daily.

## 6 weeks later...

Jim's LDL-C is 2.9 mmol/L



# GROUP DISCUSSION



WHAT DO YOU  
RECOMMEND FOR  
JIM?

- 1) Increase statin dose
- 2) Switch to another statin
- 3) Add ezetimibe
- 4) Ask Jim to diet and exercise more

# Statin initiation and monitoring

## START STATIN

At baseline check:

- CK
- ALT
- BSL

Counsel patients about what to expect when taking statins

## CHECK AT 4 - 8 WEEKS

- Lipids
- Adherence
- Lifestyle
- Adverse effects

## MEETING TARGETS

## NOT MEETING TARGETS

- Check adherence to medicines and lifestyle
- Titrate statin to MTD

If persistently not meeting targets- consider adding a second agent

# How many patients are achieving lipid targets?

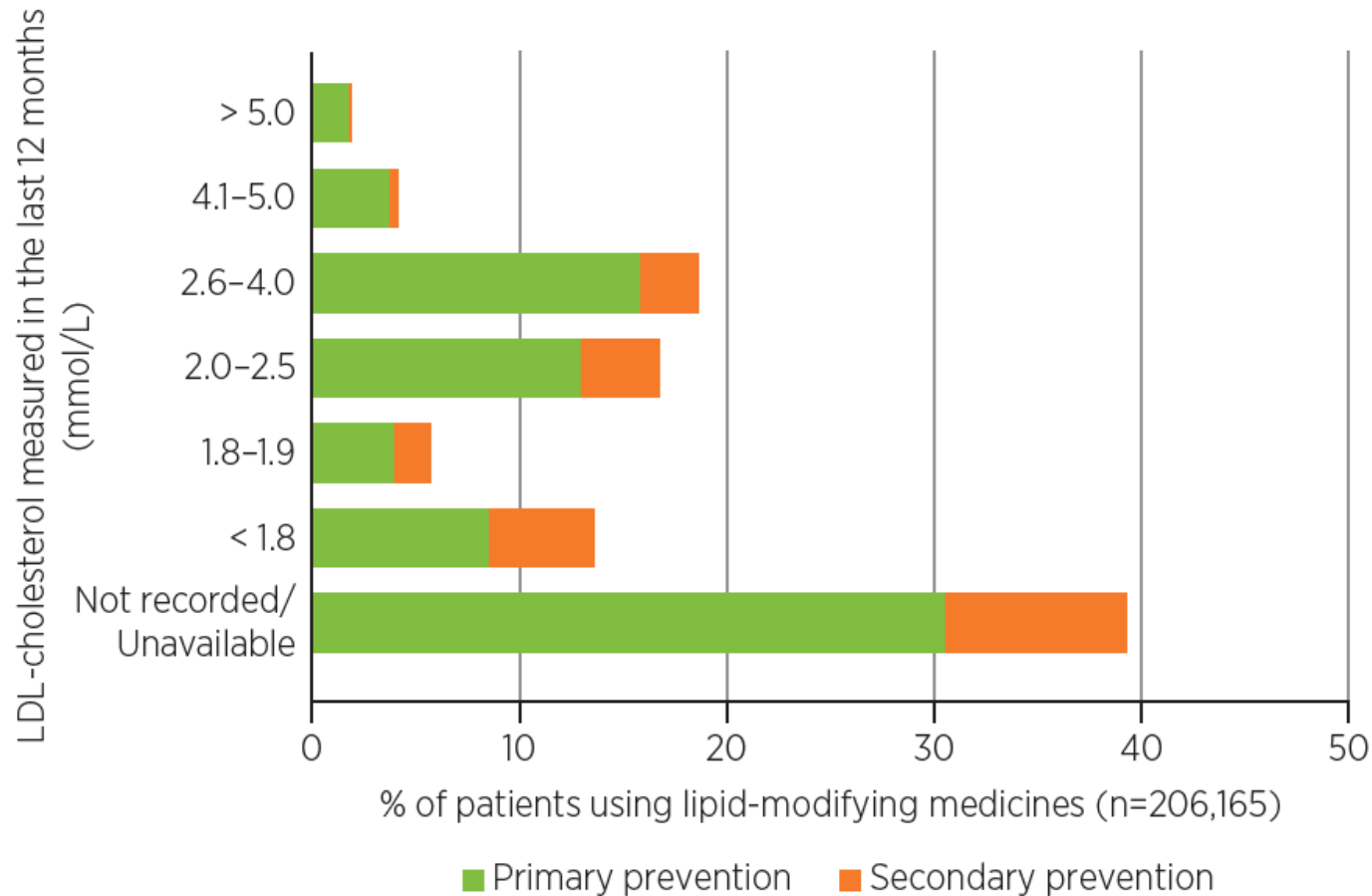


Figure 3: Proportion of patients on lipid-modifying medicines according to LDL-cholesterol and prevention status

# What is the intensity of statin treatment?

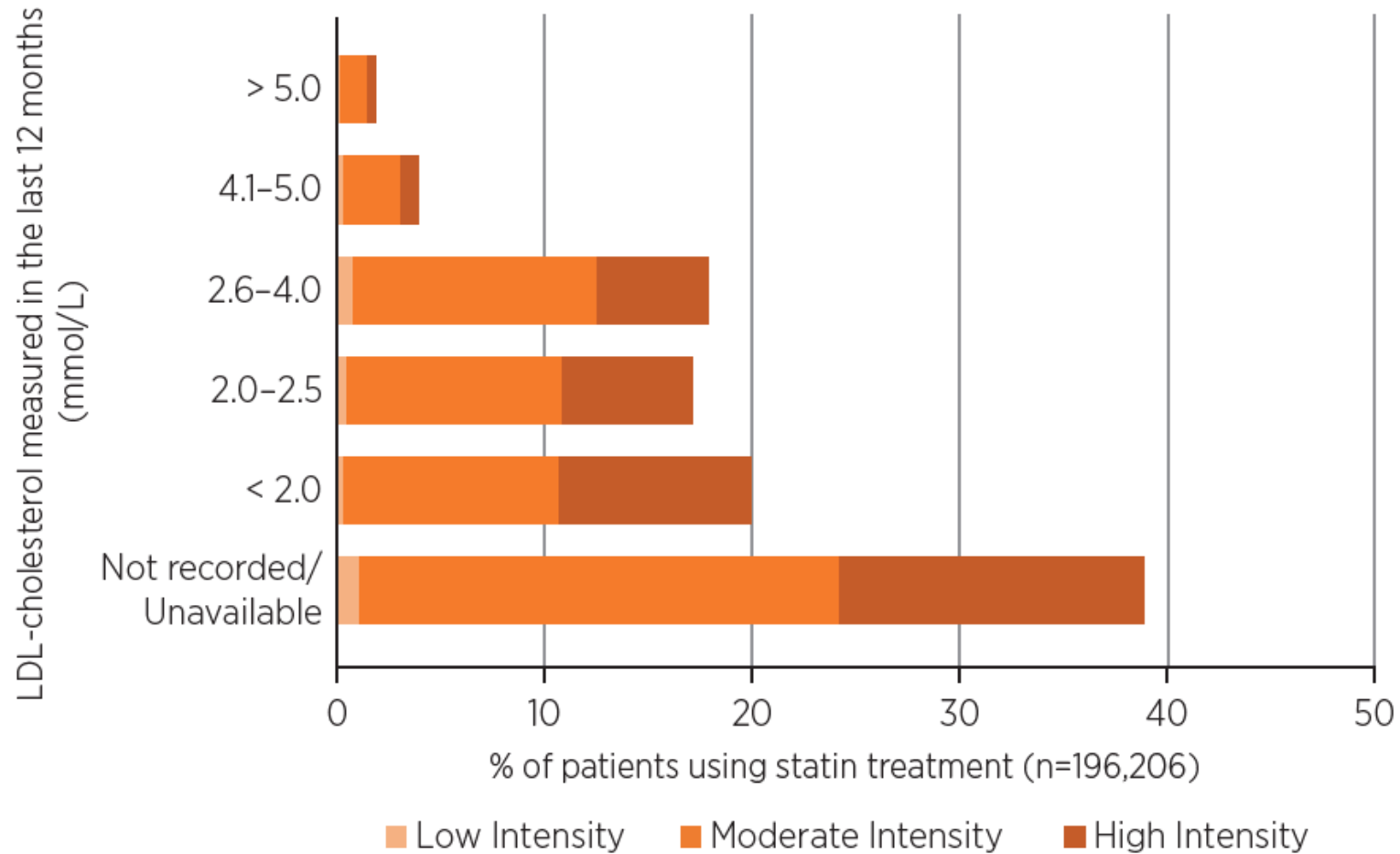


Figure 4: Proportion of patients on statin treatment according to LDL-cholesterol and statin intensity

# 6 months later...

- He is now on 40 mg atorvastatin (you up-titrated 4 months ago)
- When you ask him how things are going with his medicines he tells you he has sore muscles



# SMALL GROUP DISCUSSION

(5 mins)

WHAT DO YOU  
RECOMMEND FOR  
JIM?

## Consider...

How would you determine whether Jim's symptoms are likely to be statin-associated?

If you suspect statin-associated muscle symptoms (SAMS), what would you do to manage his symptoms?



# SAMS = Statin Associated Muscle Symptoms

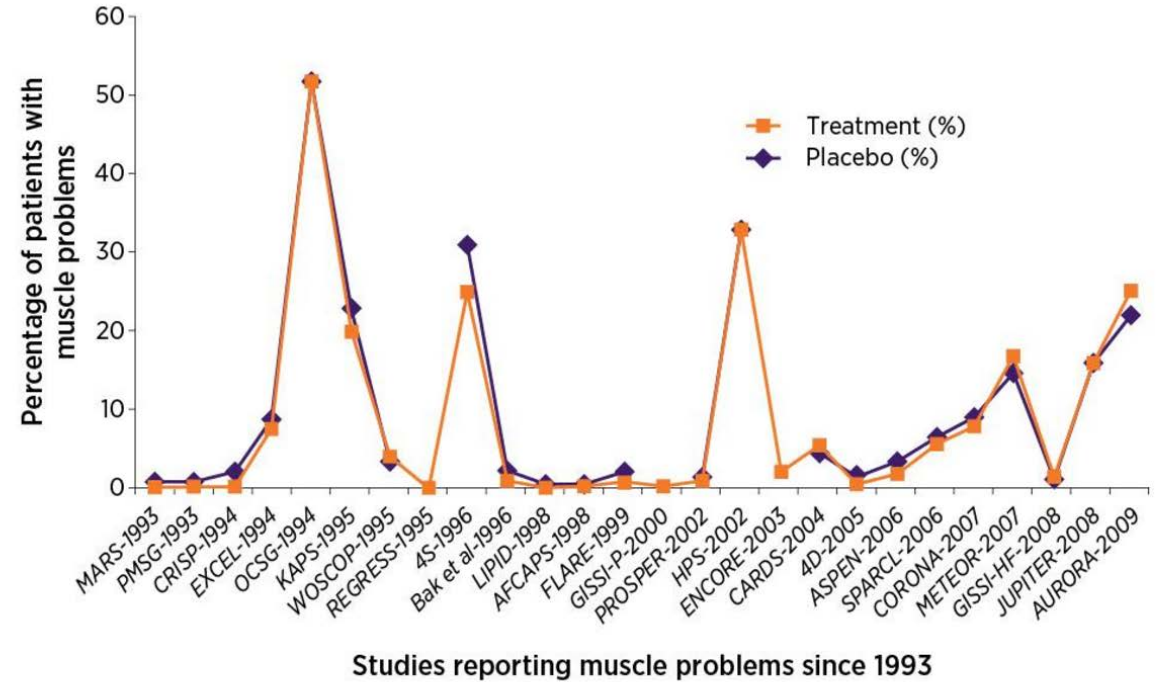
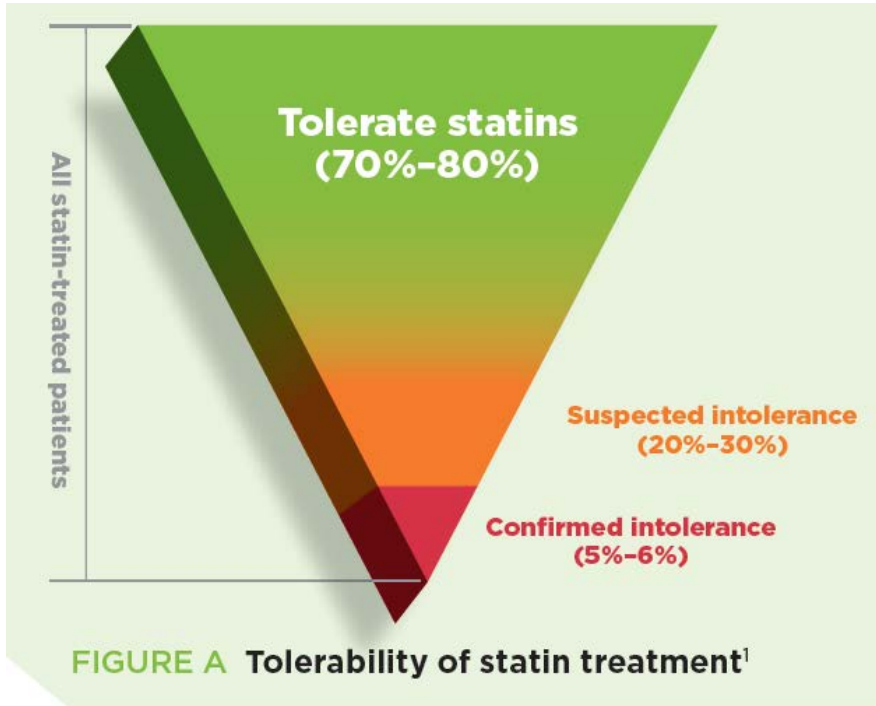
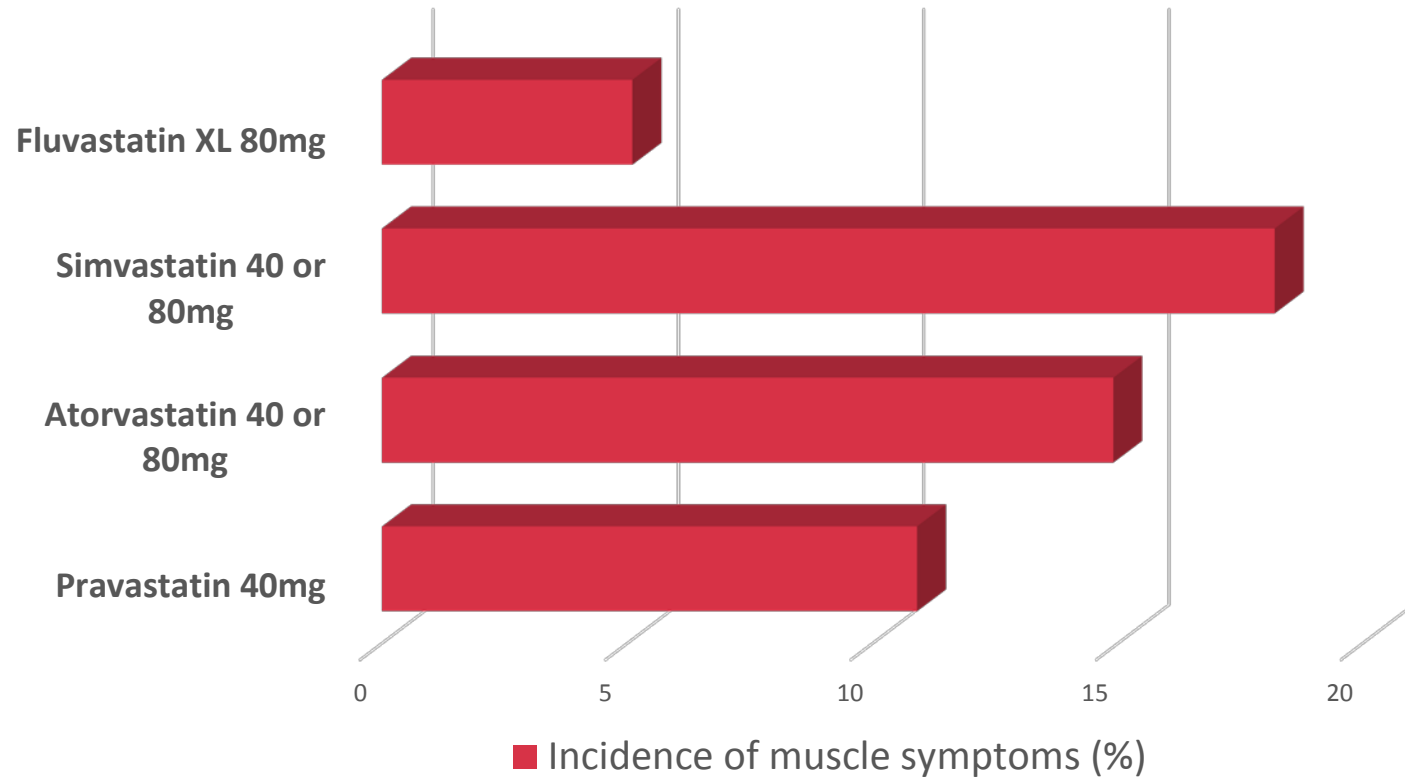


Figure 1. Muscle adverse events in statin- and placebo-treated patients in clinical trials between 1993 and 2009. Adapted from Ganga et al. 2014.<sup>12</sup>

# PRIMO study



*Figure 1: Rate of occurrence of muscular symptoms with individual statins in the PRIMO study*

# How do you know if statins are the culprit?

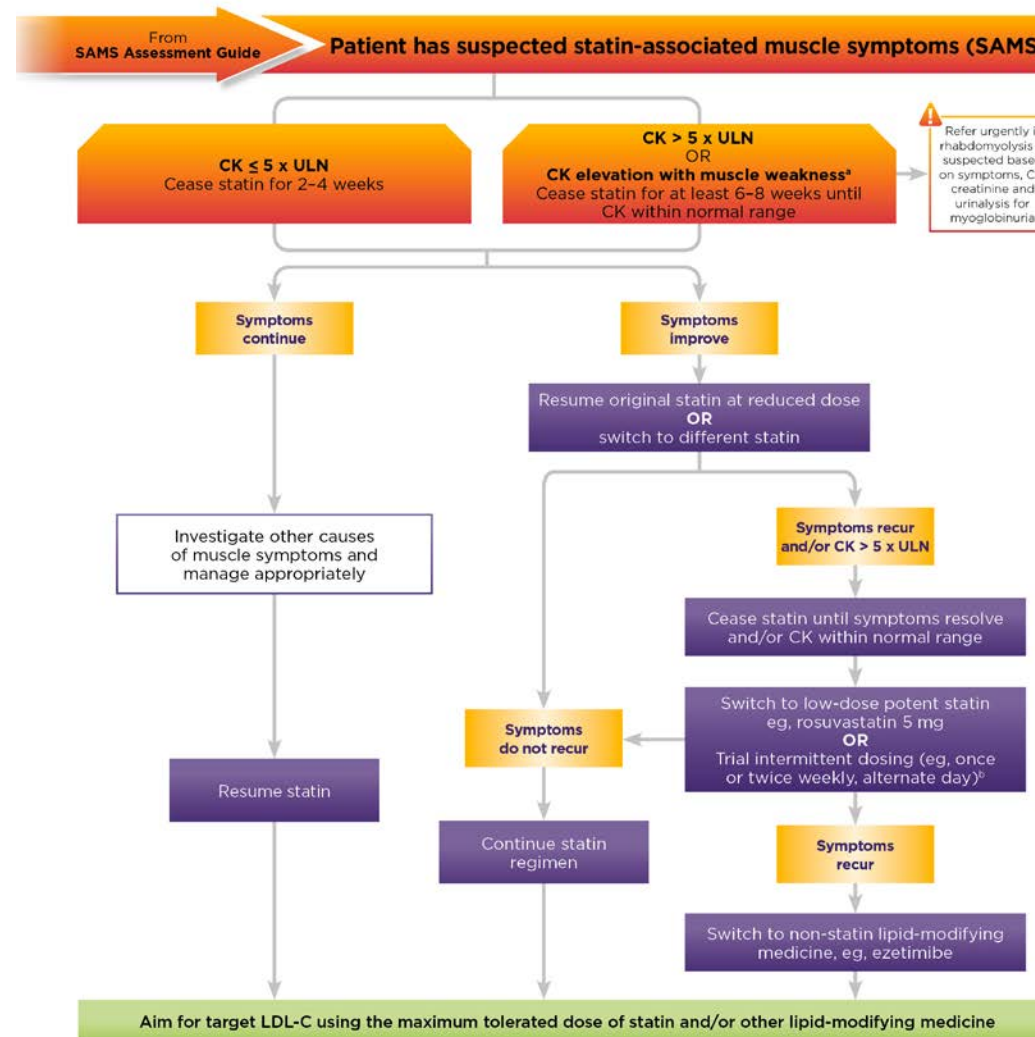
## SAMS Assessment Guide

<b>SAMS LESS LIKELY</b>		<b>SAMS MORE LIKELY</b>	
Unilateral Non-specific distribution  Tingling, twitching, shooting pain, nocturnal cramps or joint pain	<b>Nature of symptoms<sup>4,6,7</sup></b>	Bilateral Large muscle groups (eg, thighs, buttocks, calves, shoulder girdle)  Muscle ache, weakness, soreness, stiffness, cramping, tenderness or general fatigue	
Onset before statin initiation Onset > 12 weeks after statin initiation	<b>Timing of symptoms<sup>4</sup></b>	Onset 4–6 weeks after statin initiation Onset after statin dosage increase	
Non-statin causes of muscle symptoms including: <ul style="list-style-type: none"> <li>• conditions eg, hypothyroidism, polymyalgia rheumatica</li> <li>• vitamin D deficiency</li> <li>• unaccustomed/heavy physical activity</li> <li>• medicines eg, glucocorticoids, antipsychotics, immunosuppressant or antiviral agents</li> </ul>	<b>Other considerations<sup>4,7</sup></b>	Risk factors for SAMS including: <ul style="list-style-type: none"> <li>• medicine or food interactions</li> <li>• high-dose statin therapy</li> <li>• history of myopathy with other lipid-modifying medicines</li> <li>• regular vigorous physical activity</li> <li>• impaired hepatic or renal function</li> <li>• substance abuse (eg, alcohol, opioids, cocaine)</li> <li>• female</li> <li>• low BMI</li> </ul>	
	<b>CK levels<sup>4</sup></b>	Elevated (> ULN; but may also be normal) Elevated CK levels decrease after statin ceased	

If SAMS is likely, proceed to the **SAMS Management Algorithm (see overleaf)**

# SAMS Management Algorithm

## Managing SAMS – first Australian management algorithm

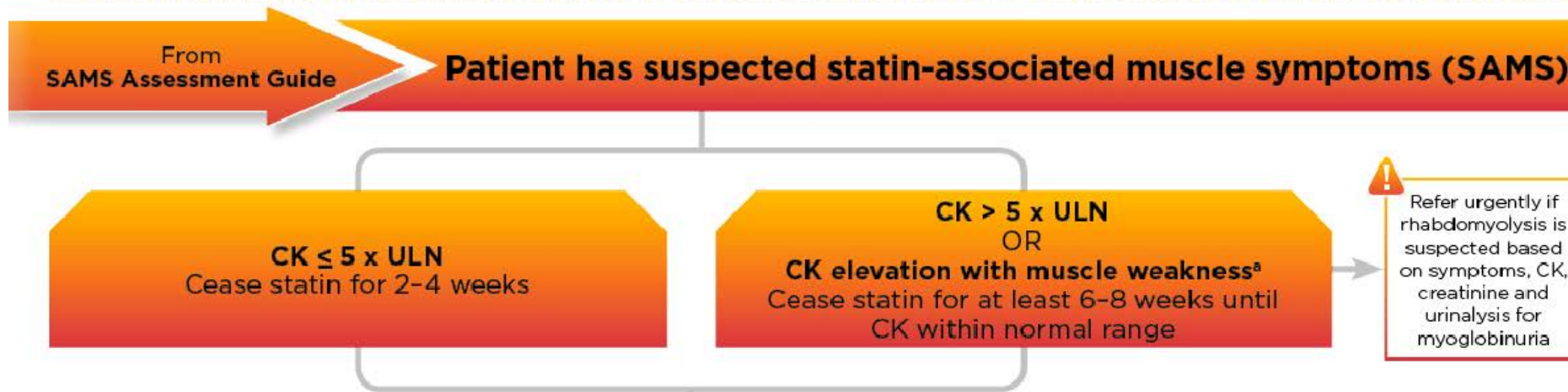


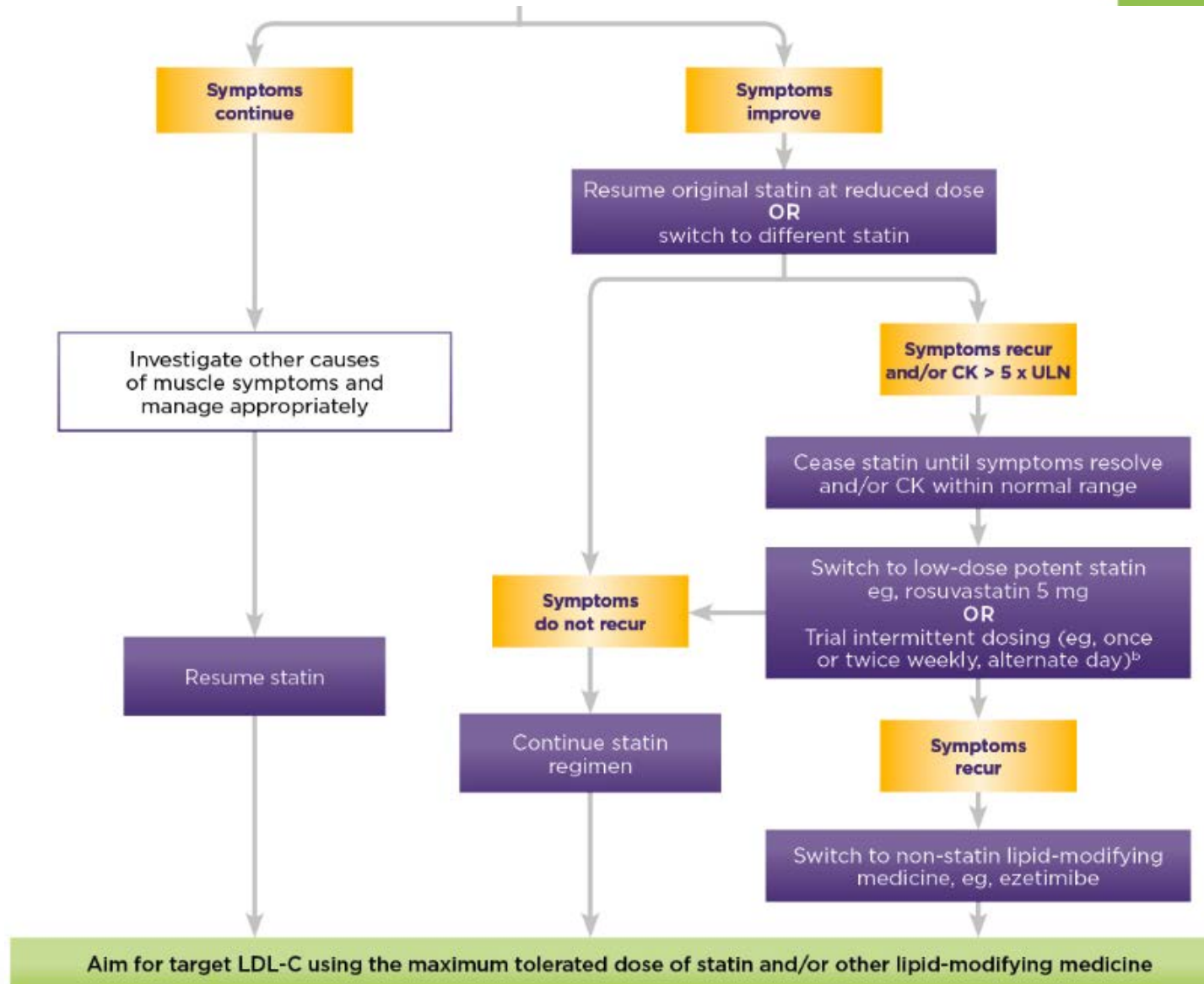
CK = creatine kinase, LDL-C = low density lipoprotein cholesterol, ULN = upper limit of normal  
 \* CK > ULN and weakness demonstrated upon physical examination. \* Higher potency statins with a long half-life are preferred for intermittent dosing eg, rosuvastatin and atorvastatin

### Acknowledgements

Developed based on the 2012 Therapeutic Guidelines: Cardiovascular and 2016 European Society of Cardiology/European Atherosclerosis Society Guidelines for the management of dyslipidaemias, with input from experts:  
 Assoc Prof David Colquhoun, Prof Ian Hamilton-Craig, Prof Mark Harris, Assoc Prof Karam Kostner, Prof Leonard Kritharides, Prof Mark Nelson, Dr Daniel Scherer, Assoc Prof David Sullivan, Prof Andrew Tonkin, Mr Garth Birdsey, Dr Chris Helms

# SAMS Management Algorithm





CK = creatine kinase, LDL-C = low density lipoprotein cholesterol, ULN = upper limit of normal  
<sup>a</sup> CK > ULN and weakness demonstrated upon physical examination. <sup>b</sup> Higher potency statins with a long half-life are preferred for intermittent dosing eg, rosuvastatin and atorvastatin

# SUMMARY

- ▶ Assess absolute CV risk before prescribing lipid-modifying medicines
- ▶ Optimise LDL-C lowering by adequately trialling statin therapy before adding a second agent
- ▶ True statin intolerance is uncommon. Use a systematic approach to assess suspected statin intolerance

# Virtual educational visits

- ▶ NPS MedicineWise now offers web-enabled virtual visits using Skype for Business
- ▶ Useful for practices or GPs who missed out on an educational visit. Or who find it difficult to schedule a visit at a date and time that suits them
- ▶ Contact your local Clinical Service Specialist to organize or our Program Engagement team:  
Phone: 02 8217 8700  
Email: [bookavisit@nps.org.au](mailto:bookavisit@nps.org.au)



Questions?