STATINS: OPTIMISING THERAPY, ADDRESSING INTOLERANCE

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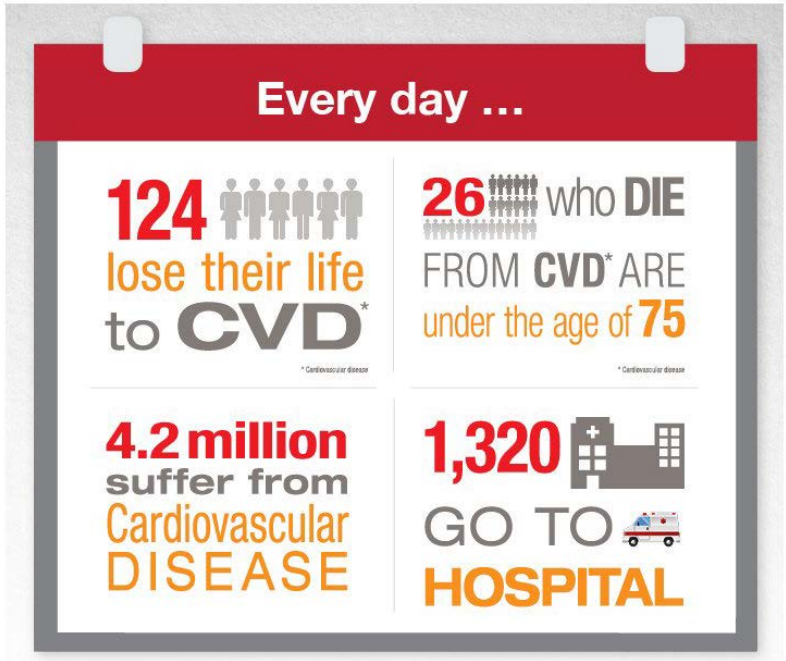
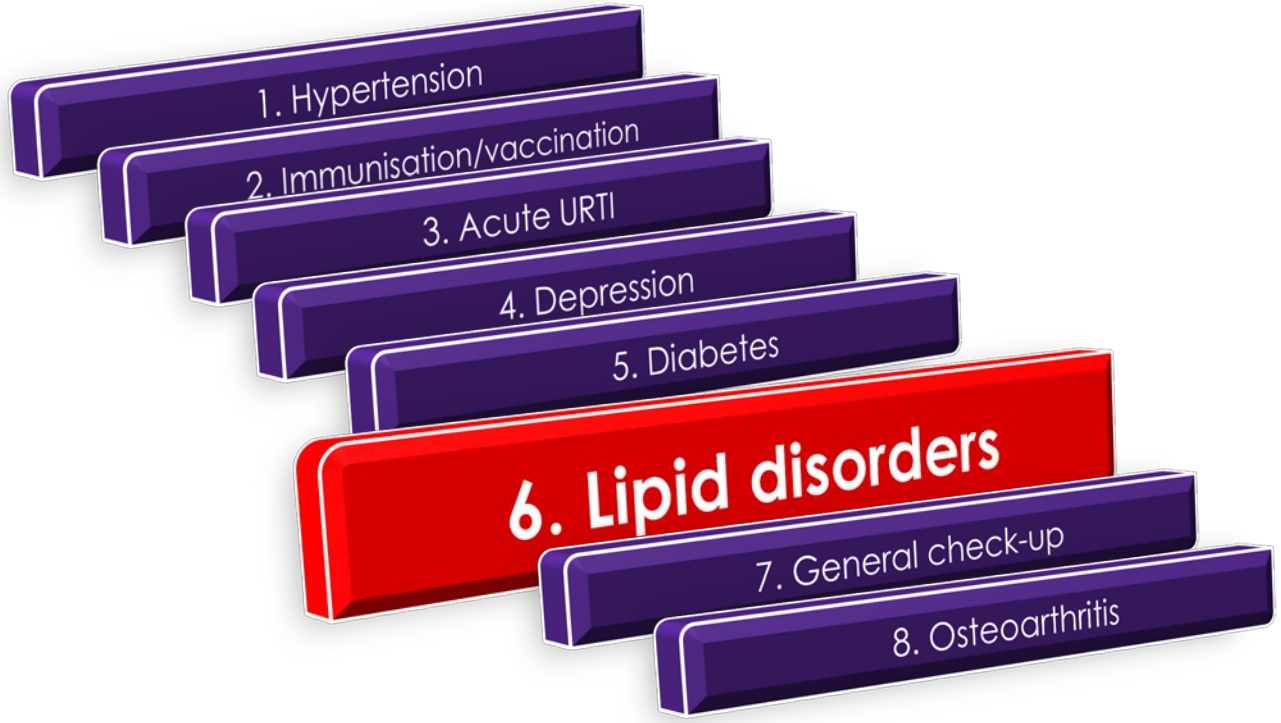
Cardiovascular disease





Most frequently managed conditions in Australian general practice

https://twitter.com/heartaust/status/781370301883887616

Common general practice presentations and publication frequency. Volume 42, No.1, January/February 2013 Pages 65-68

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5 Reasons Why You
SHOULD
NOT Take
Statins
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STATINS
DO HARM.
You are better off
without them!
Alternative-Doctor.com
Dr. Keith Scott-Mumby


ALERT!
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28
Tablets
STATIN
28
Tablets


Muscle Damage
Cholesterol Drug


The DANGERS of STATIN DRUGS
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MedicineInsight report visit

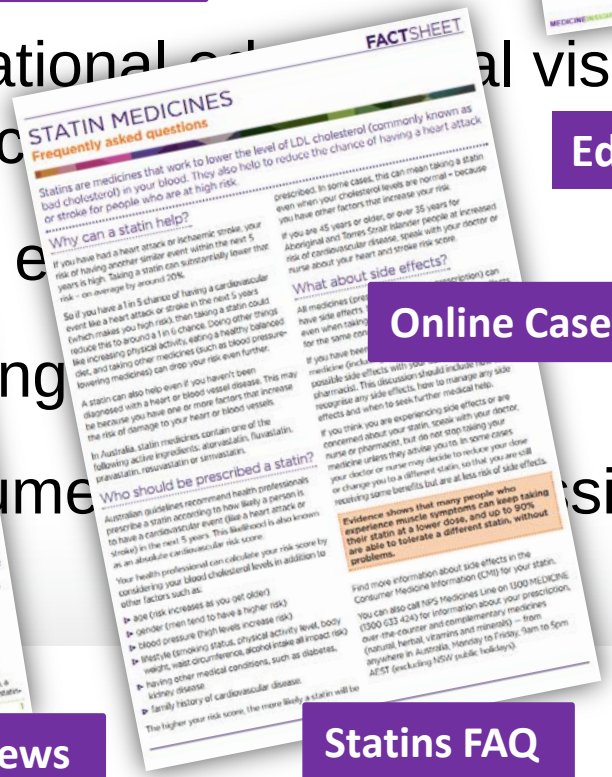
Pharmacy visit

Small group visit

Pharmacy Practice Review

Multifacet[illegible] national [illegible]al visiting program ta[illegible]

Educational visits



Online Case Study

Clinical e-Audit

nps.org.au/statins

MedicineWise News

Statins FAQ

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CASE STUDY

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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

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Meet Jim

Blood test results (non-fasting)

Lipid profile		Target
TC	6.4 mmol/L	< 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		**Normal range**
Blood glucose	5.0 mmol/L	< 5.5 mmol/L
HbA_{1c}	43.2 mmol/mol 6.1%	< 48 mmol/mol < 6.5%

Examination

BP

136/86 mmHg

BMI

32 kg/m²

Waist circumference

108 cm

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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

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

Blood test results (non-fasting)

Lipid profile		Target
TC	6.4 mmol/L	< 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		**Normal range**
Blood glucose	5.0 mmol/L	< 5.5 mmol/L
HbA_{1c}	43.2 mmol/mol 6.1%	< 48 mmol/mol < 6.5%

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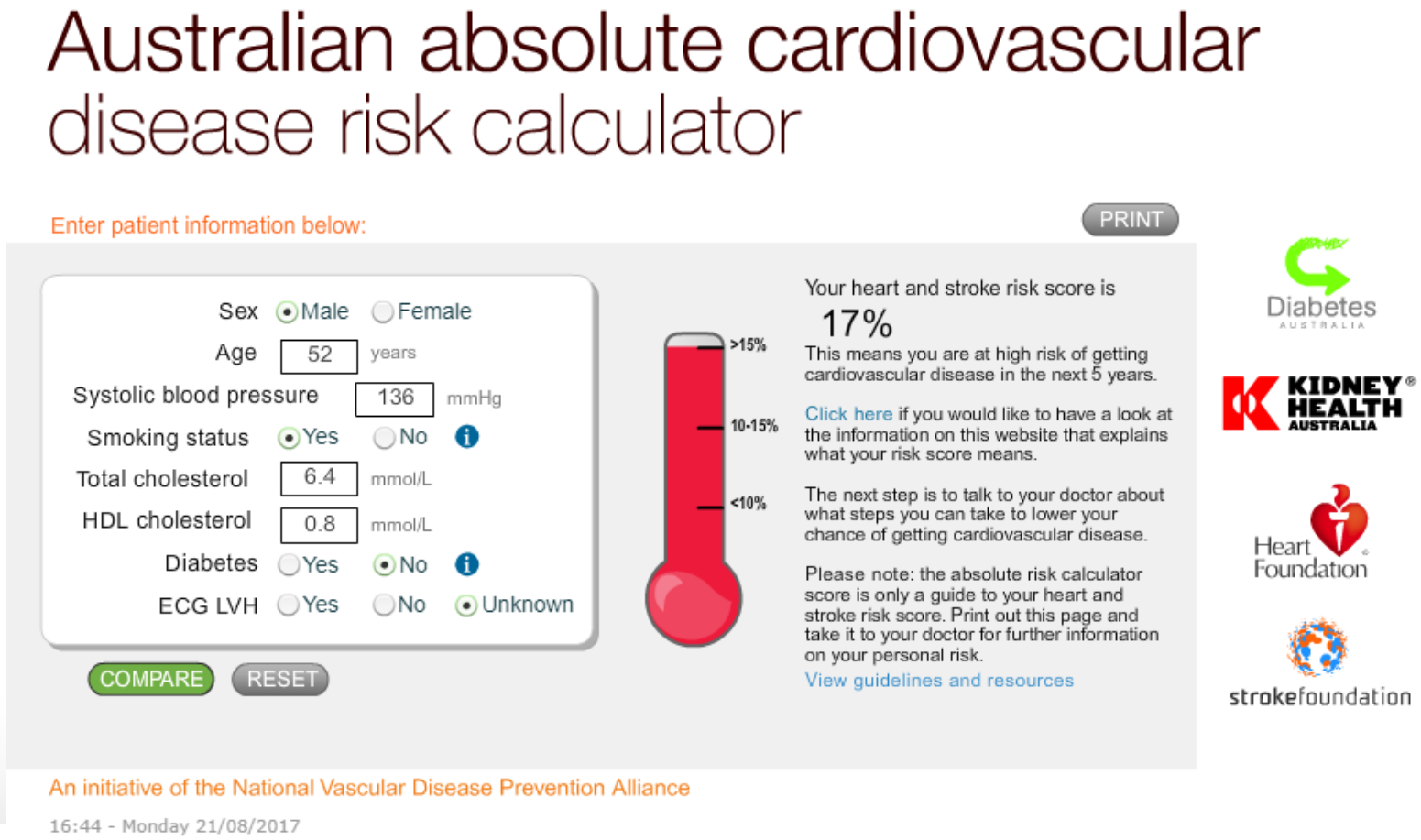
Jim’s absolute risk profile



Diabetes Australia

Kidney Health Australia

Heart Foundation

strokefoundation

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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.

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Why treat high risk patients?

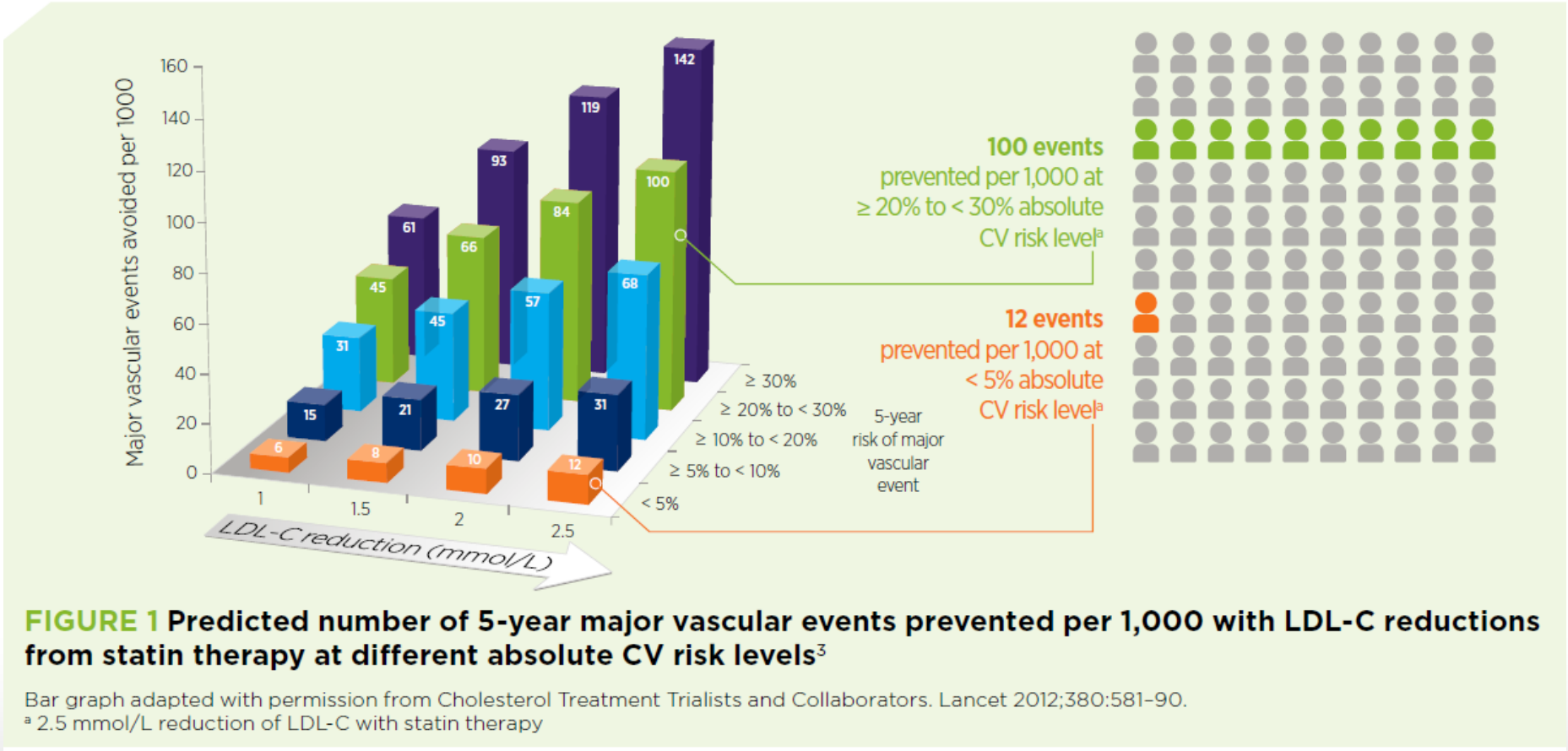

FIGURE 1 Predicted number of 5-year major vascular events prevented per 1,000 with LDL-C reductions from statin therapy at different absolute CV risk levels[3]

Bar graph adapted with permission from Cholesterol Treatment Trialists and Collaborators. Lancet 2012;380:581–90.
[a] 2.5 mmol/L reduction of LDL-C with statin therapy

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High risk patients missing out on statins

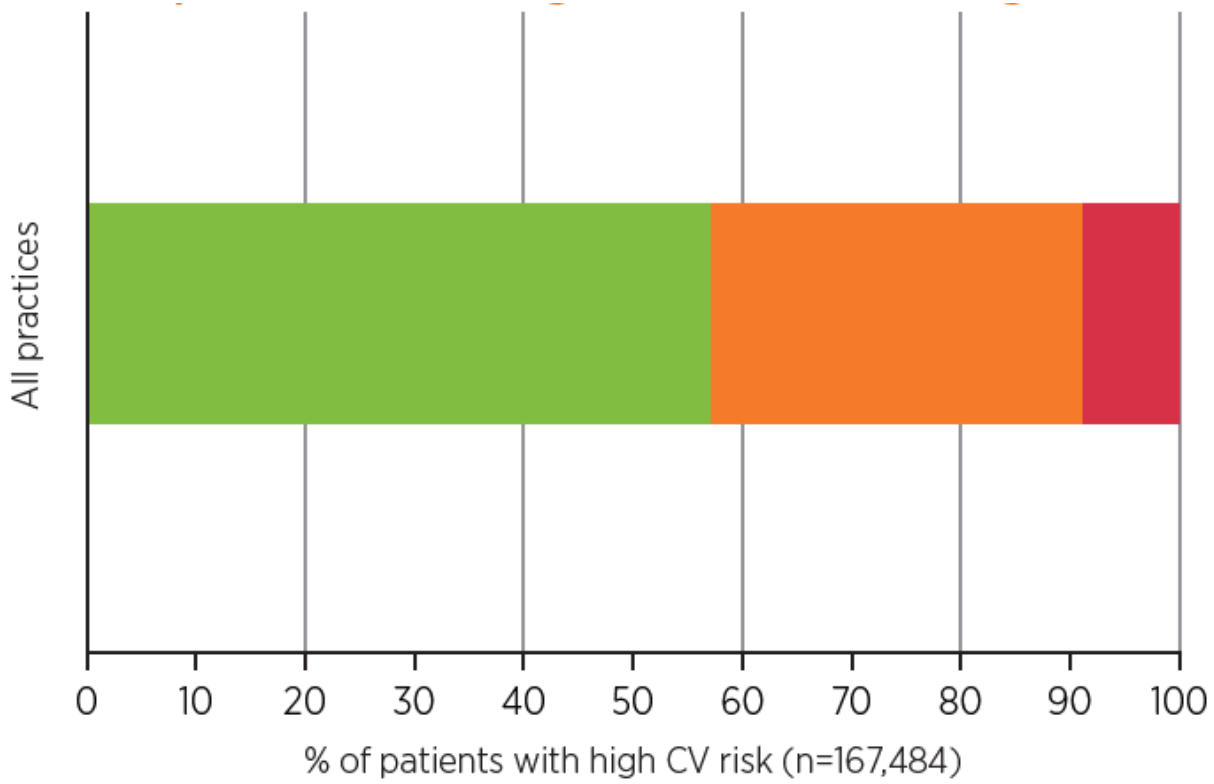

Figure 1: Proportion of patients aged 45–74 years at high CV risk according to statin treatment and prevention status

Australian general practice: MedicineInsight data; 2017

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

Would you recommend a lipid-modifying medicine?

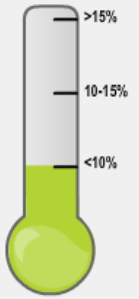
Australian absolute cardiovascular disease risk calculator

Enter patient information below:

PRINT

Sex	◉ Male ○ Female	
Age	52	years
Systolic blood pressure	120	mmHg
Smoking status	○ Yes ◉ No	
Total cholesterol	6.4	mmol/L
HDL cholesterol	0.8	mmol/L
Diabetes	○ Yes ◉ No	
ECG LVH	○ Yes ○ No ◉ Unknown	

COMPARE RESET



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

An initiative of the National Vascular Disease Prevention Alliance

Diabetes Australia

Kidney Health Australia

Heart Foundation

strokefoundation

Blood test results (non-fasting)

Lipid profile		Target
TC	6.4 mmol/L	< 4.0 mmol/L
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Overprescribing of statins?

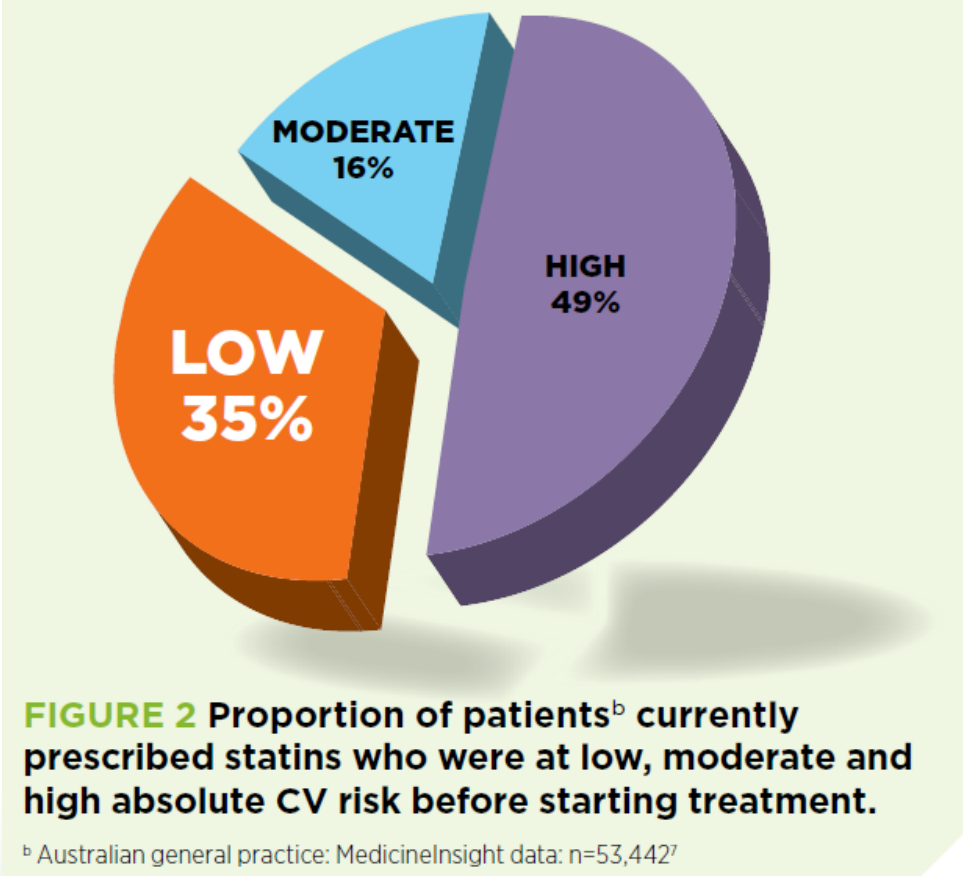

FIGURE 2 Proportion of patients[b] currently prescribed statins who were at low, moderate and high absolute CV risk before starting treatment.

[b] Australian general practice: MedicineInsight data: n=53,442[7]

Australian general practice: MedicineInsight data; 2017

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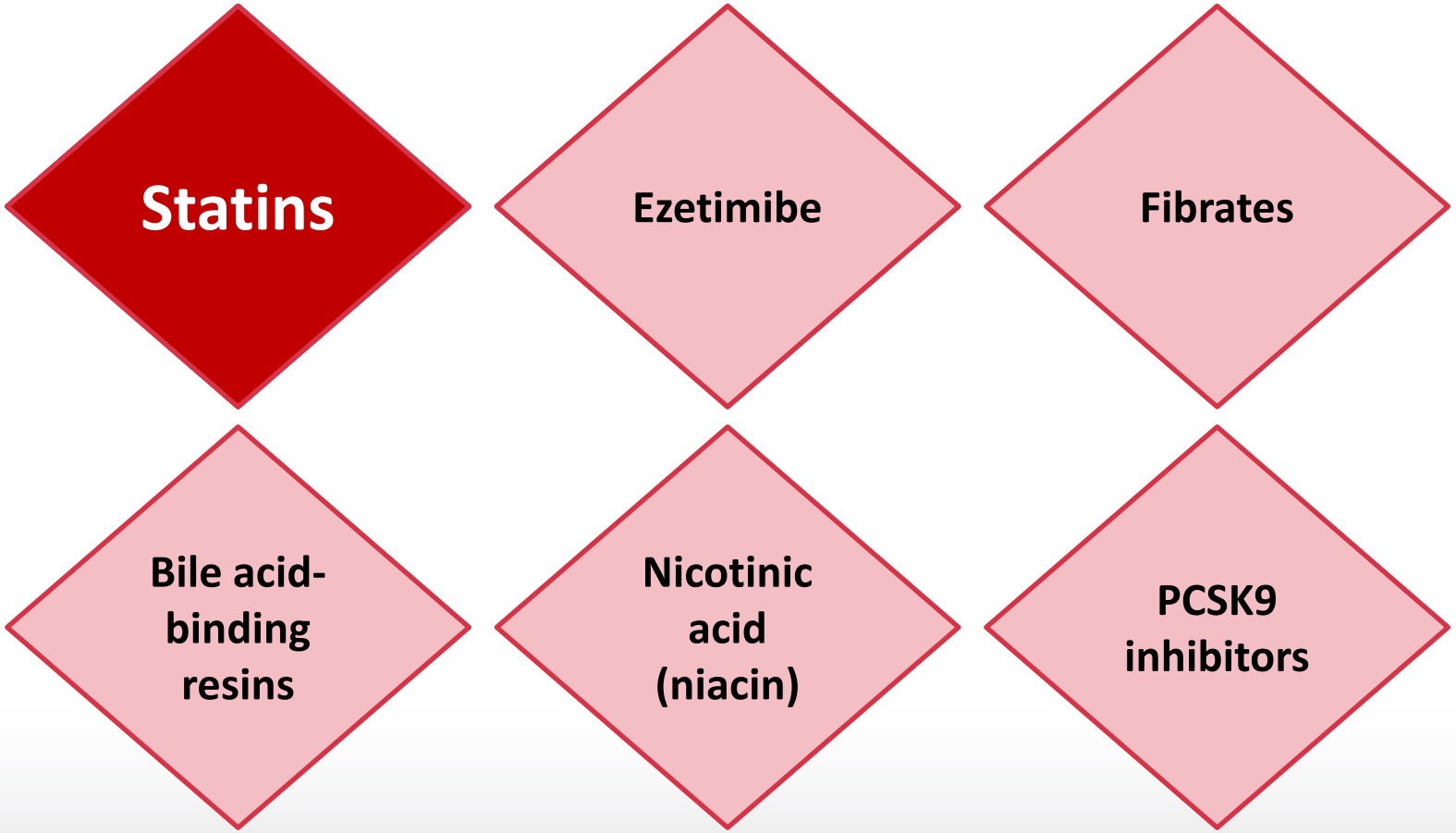
Which lipid-modifying therapy to prescribe?



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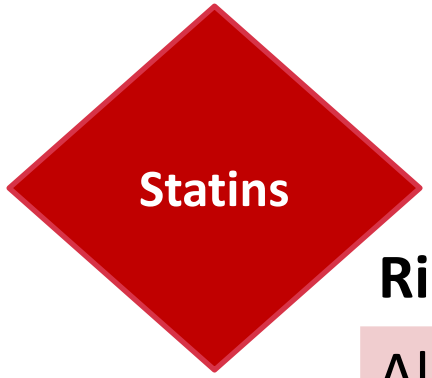
Statins are still first line



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%

CTT collaboration Lancet 2005; 366: 1267-1278

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LDL-C: ‘the lower the better’?

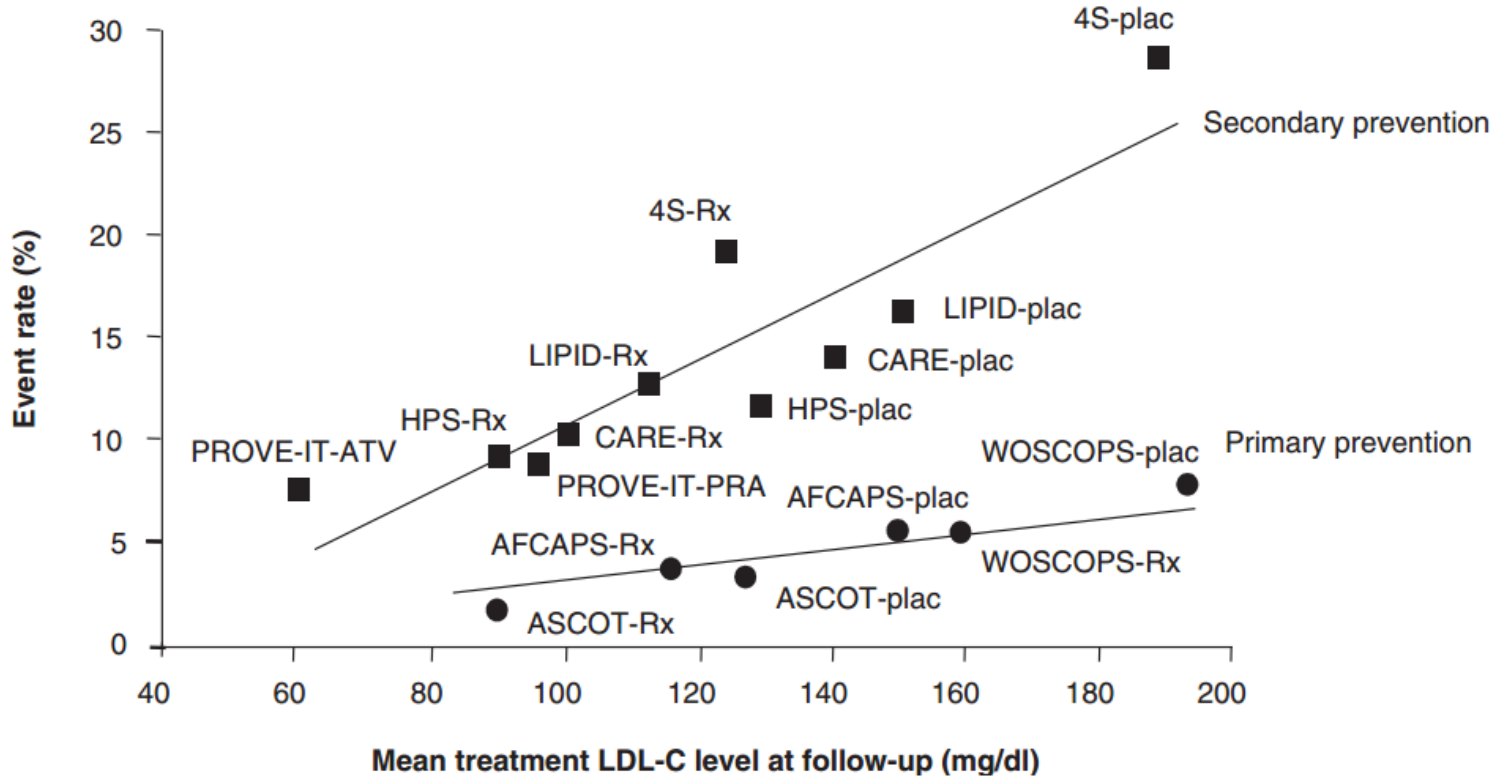

Figure 1. Relationship between on-treatment LDL-C and cardiovascular events in landmark statin trials.

Expert Opin. Emerg. Drugs (2004) 9(2):269-279

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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

European Heart Journal (2017) 0, 1–14 doi:10.1093/eurheartj/ehx144

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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[c]
Non-HDL-C	< 2.5 mmol/L
TG	< 2.0 mmol/L

NVDPA. Guidelines for the management of absolute cardiovascular disease risk. 2012.

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Dose equivalency

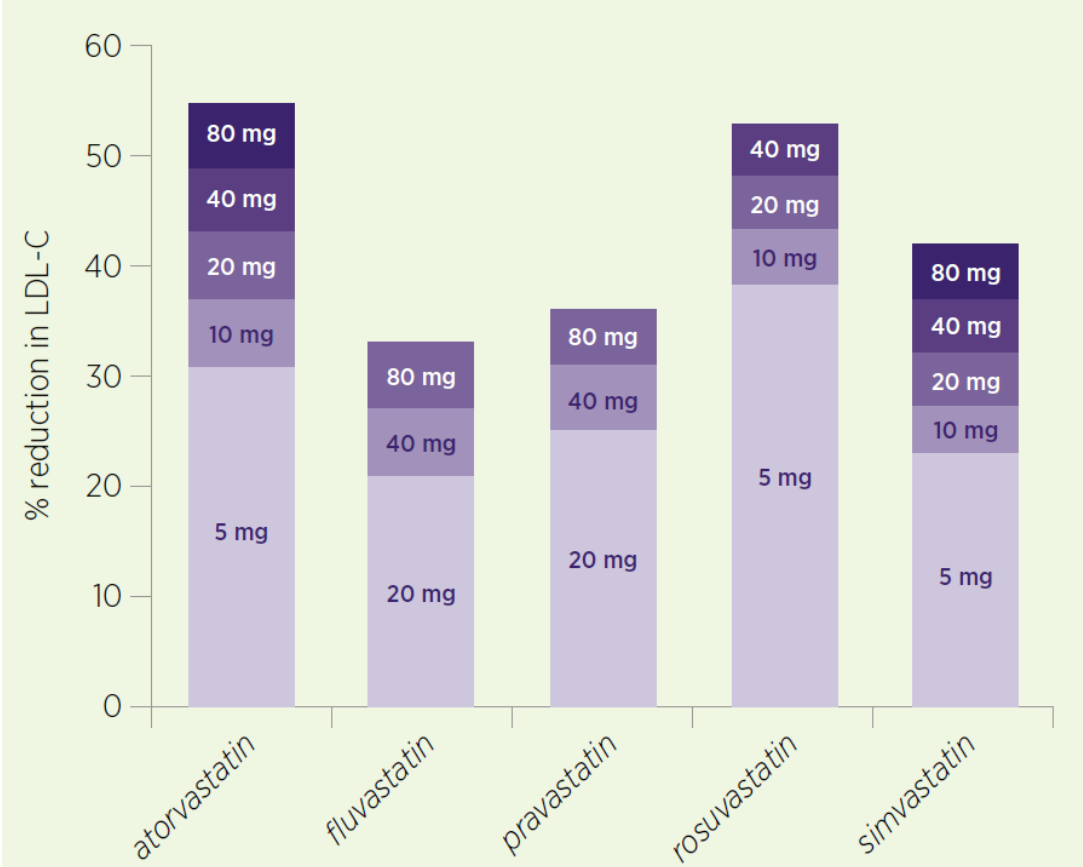

FIGURE 3 Effect of statins on LDL-C according to dose[18]

Adapted with permission from Law MR, et al. BMJ 2003;326:1423–7

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Drug interactions (CYP450)

TABLE 1 Examples of cytochrome P450-mediated statin medicine interactions[17]

STATIN	METABOLISED BY	STATIN CONCENTRATION MAY BE INCREASED BY	STATIN CONCENTRATION MAY BE DECREASED BY
Atorvastatin **Simvastatin**	CYP3A4 (main)	CYP3A4 inhibitors • Azole antifungals (all) • Calcium channel blockers (only diltiazem, verapamil) • Fluvoxamine • Grapefruit juice • HIV-protease inhibitor antiretrovirals (all) • Macrolide antibacterials (only clarithromycin, erythromycin) • Ticagrelor	CYP3A4 inducers • Antiepileptics (some eg, carbamazepine, phenytoin) • HIV-protease inhibitor antiretrovirals (only ritonavir, tipranavir) • Rifampicin • St John's wort
Fluvastatin	CYP2C9 (main) CYP3A4 (lesser extent)	CYP2C9 inhibitors • Amiodarone • Azole antifungals (only fluconazole, voriconazole) • SSRIs (only fluoxetine, fluvoxamine) CYP3A4 inhibitors (see above)	CYP2C9 inducers • Rifampicin • St John's wort CYP3A4 inducers (see above)
Pravastatin **Rosuvastatin**	Not significantly metabolised by CYP enzymes		

Australian Medicines Handbook. Adelaide: Australian Medicines Handbook Pty Ltd, 2017.

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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

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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

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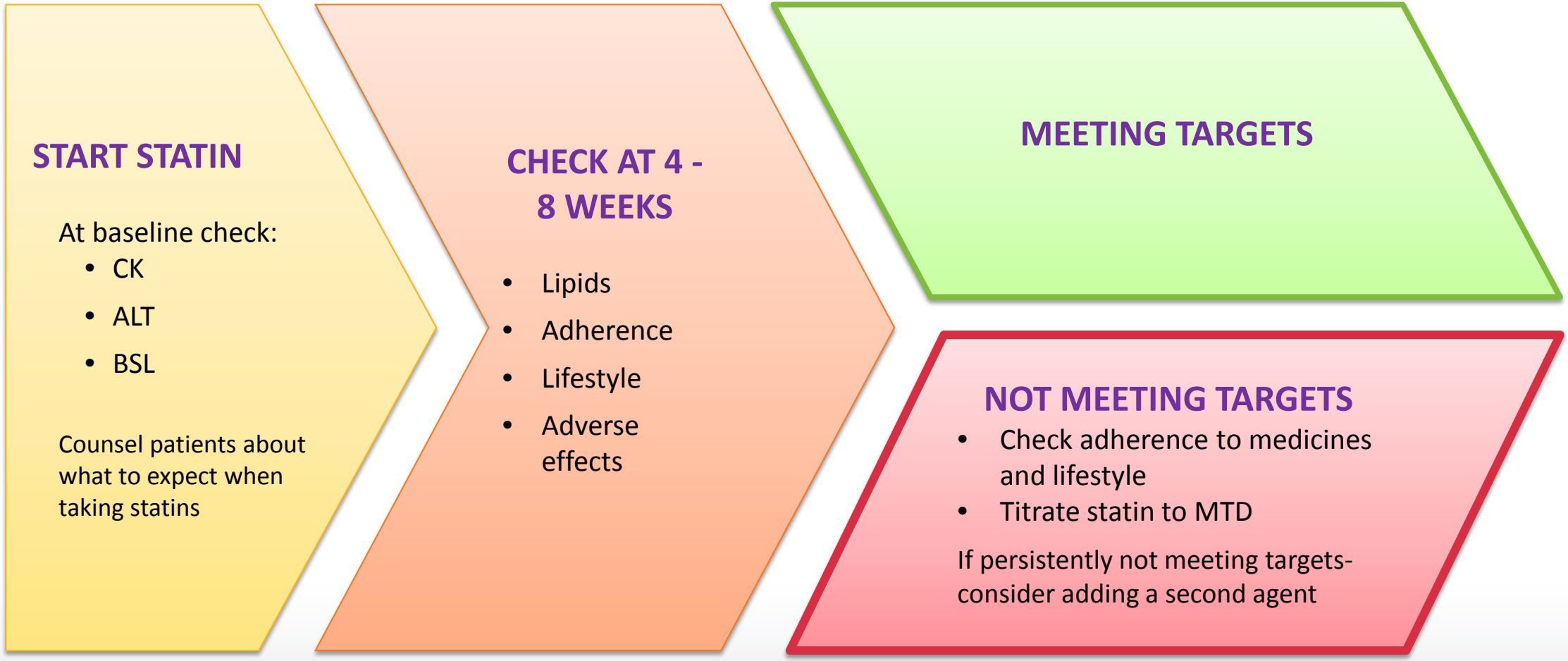
Statin initiation and monitoring



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How many patients are achieving lipid targets?

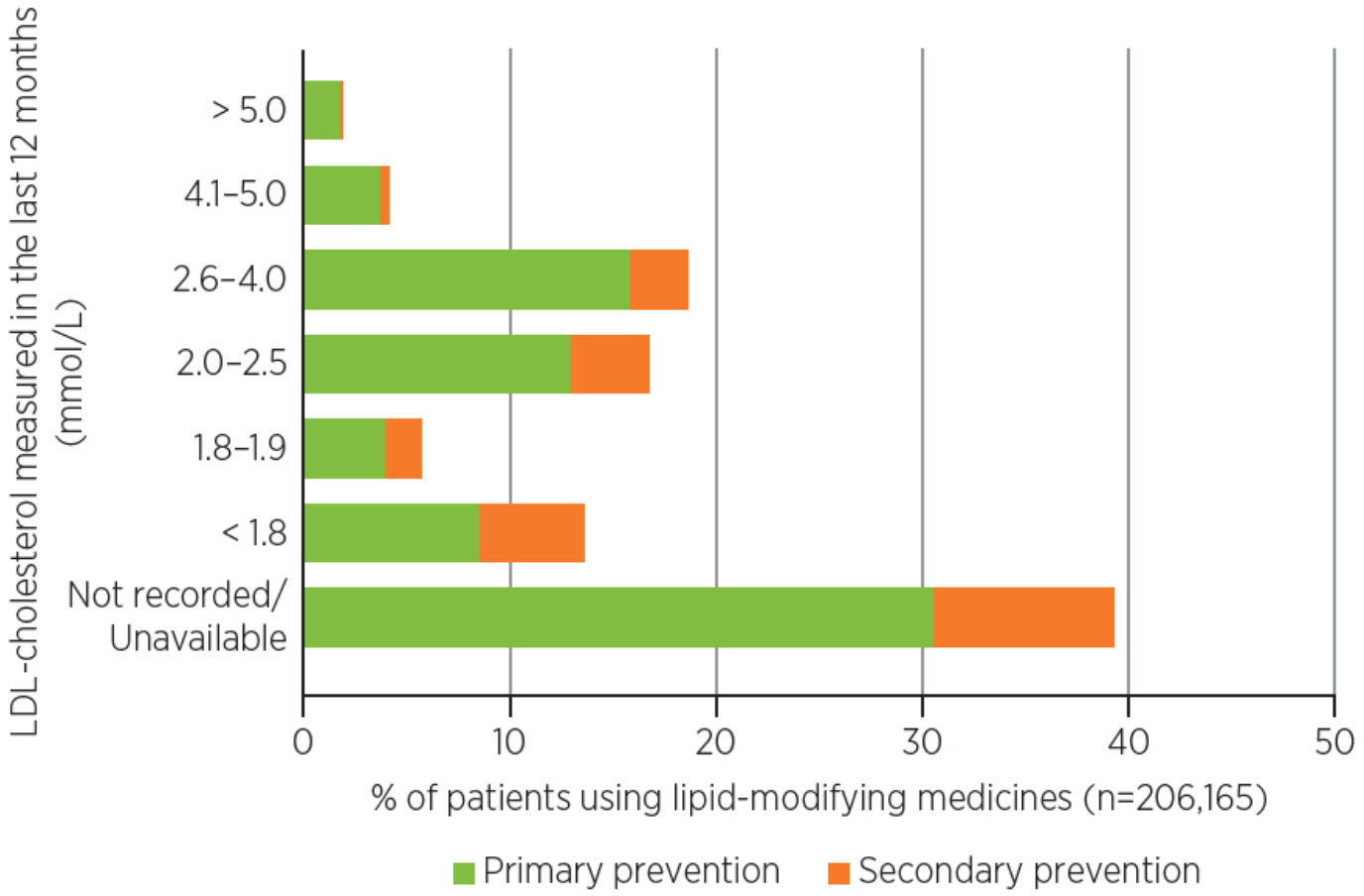

Figure 3: Proportion of patients on lipid-modifying medicines according to LDL-cholesterol and prevention status

Australian general practice: MedicineInsight data; 2017

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What is the intensity of statin treatment?

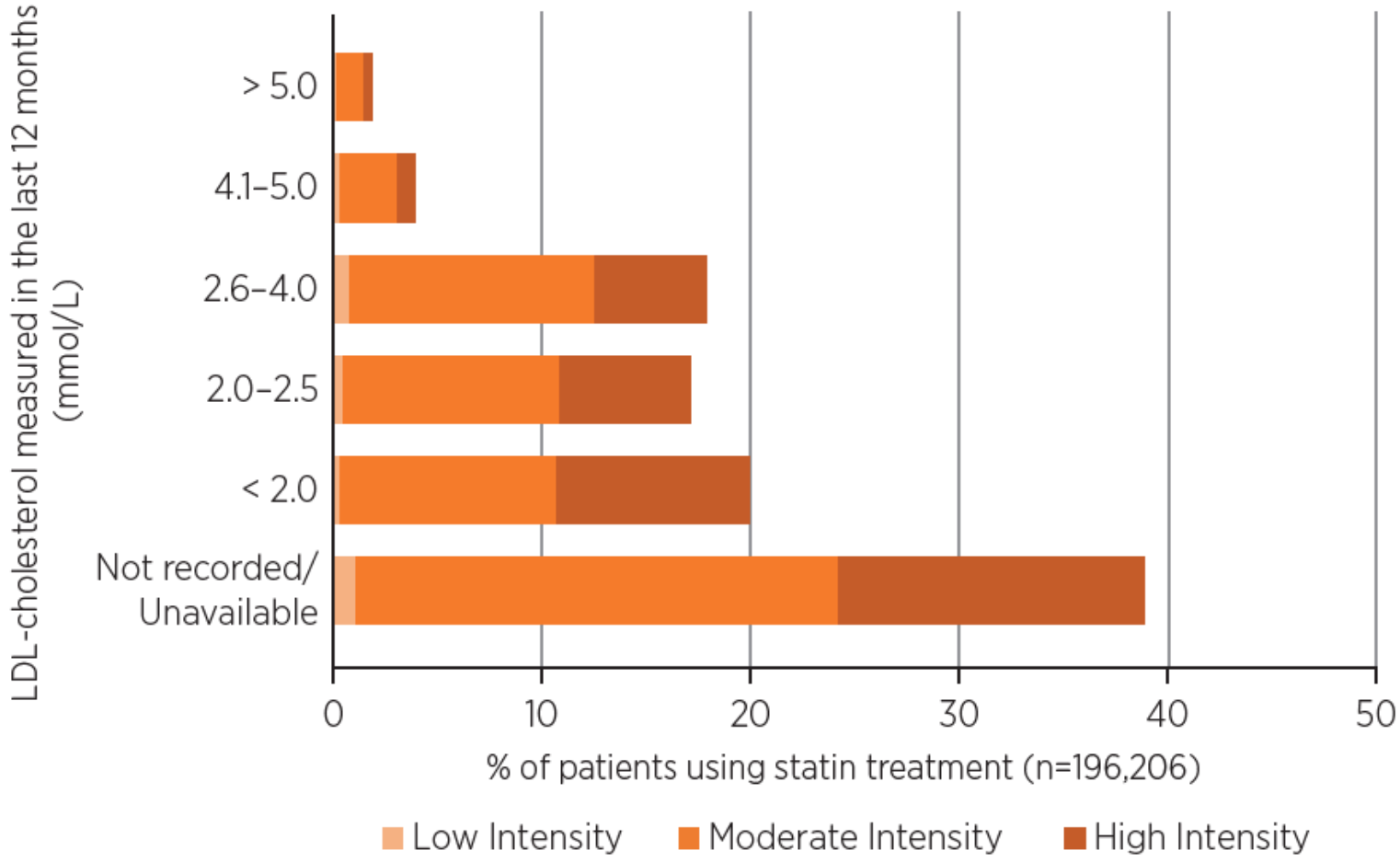

Figure 4: Proportion of patients on statin treatment according to LDL-cholesterol and statin intensity

Australian general practice: MedicineInsight data; 2017

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?

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SAMS = Statin Associated Muscle Symptoms

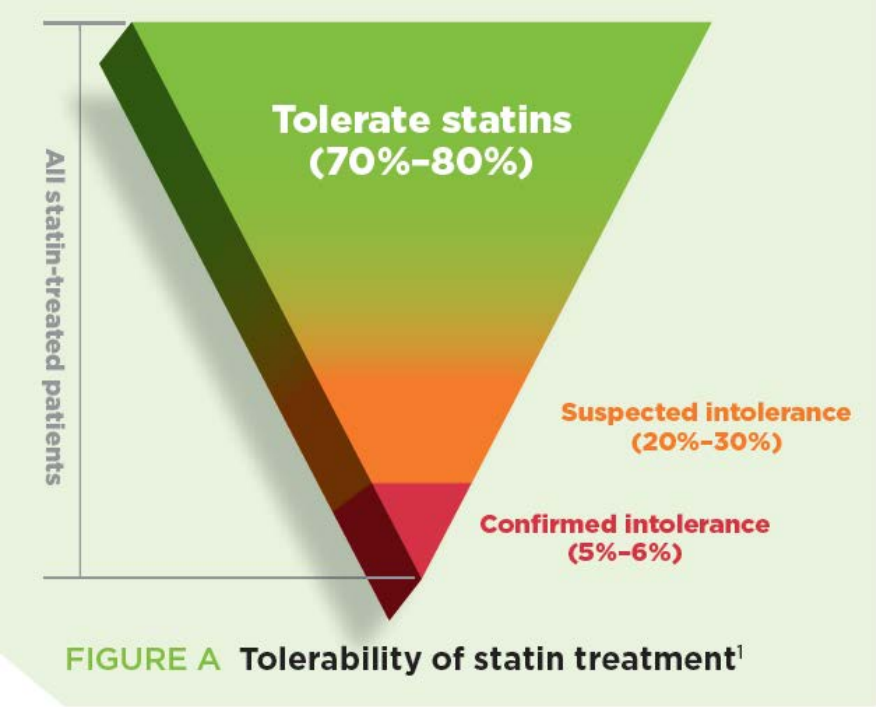

FIGURE A **Tolerability of statin treatment**[1]

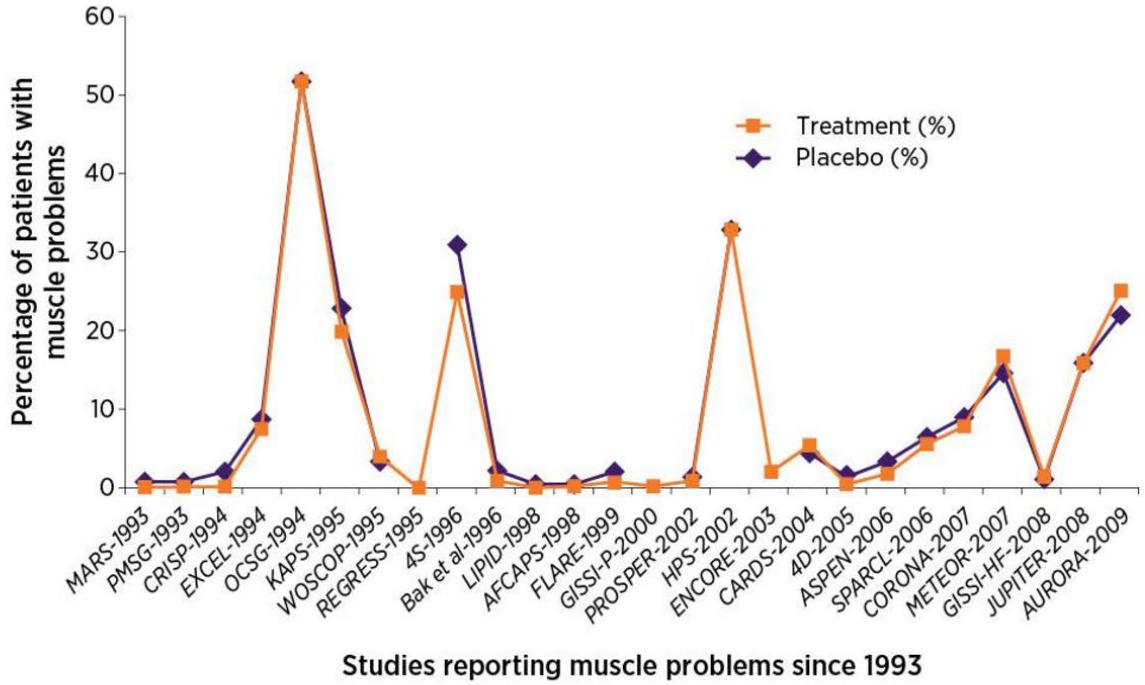

Figure 1. Muscle adverse events in statin- and placebo-treated patients in clinical trials between 1993 and 2009. Adapted from Ganga et al. 2014.[12]

Am Heart J. 2014 Jul;168(1):6-15. doi: 10.1016/j.ahj.2014.03.019.

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PRIMO study

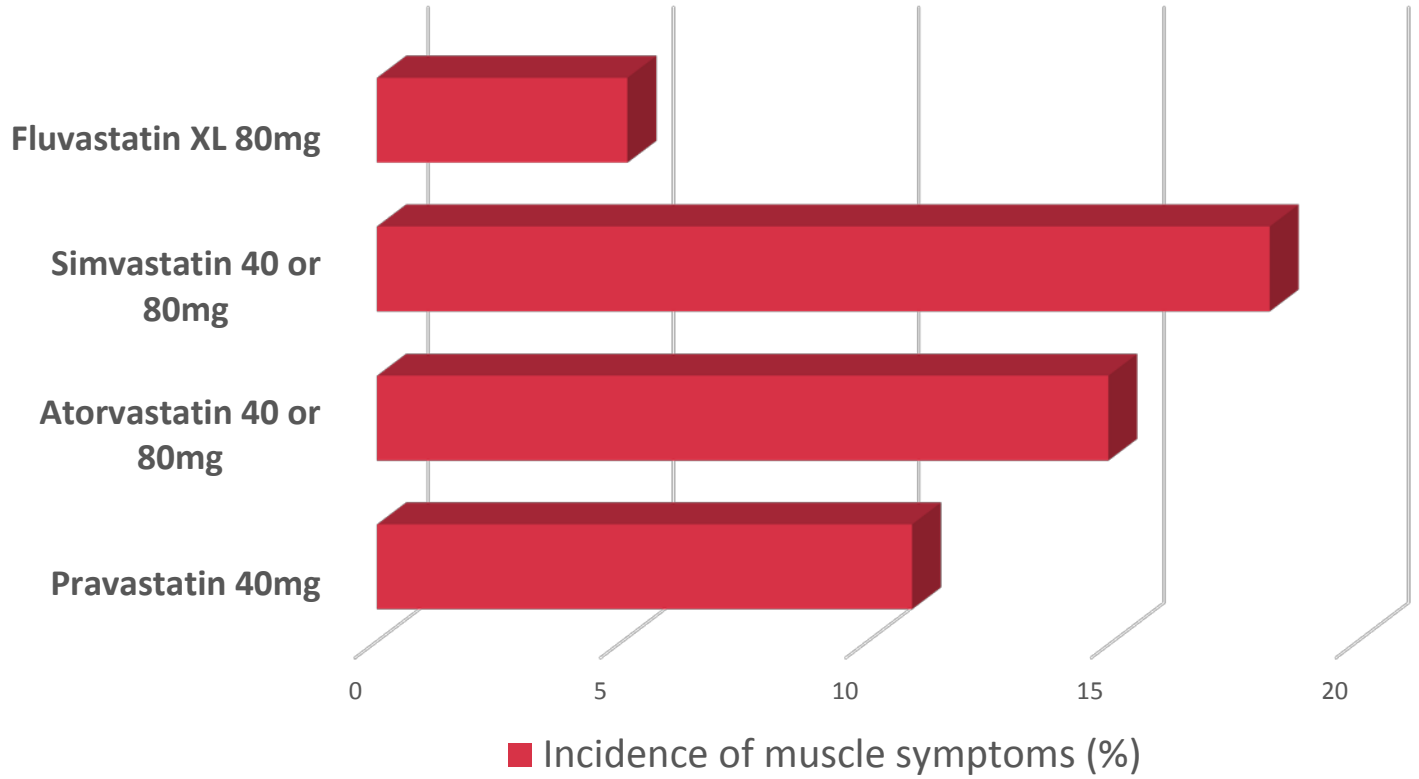

Figure 1: Rate of occurrence of muscular symptoms with individual statins in the PRIMO study

Cardiovasc Drugs Ther. 2005 Dec;19(6):403-14.

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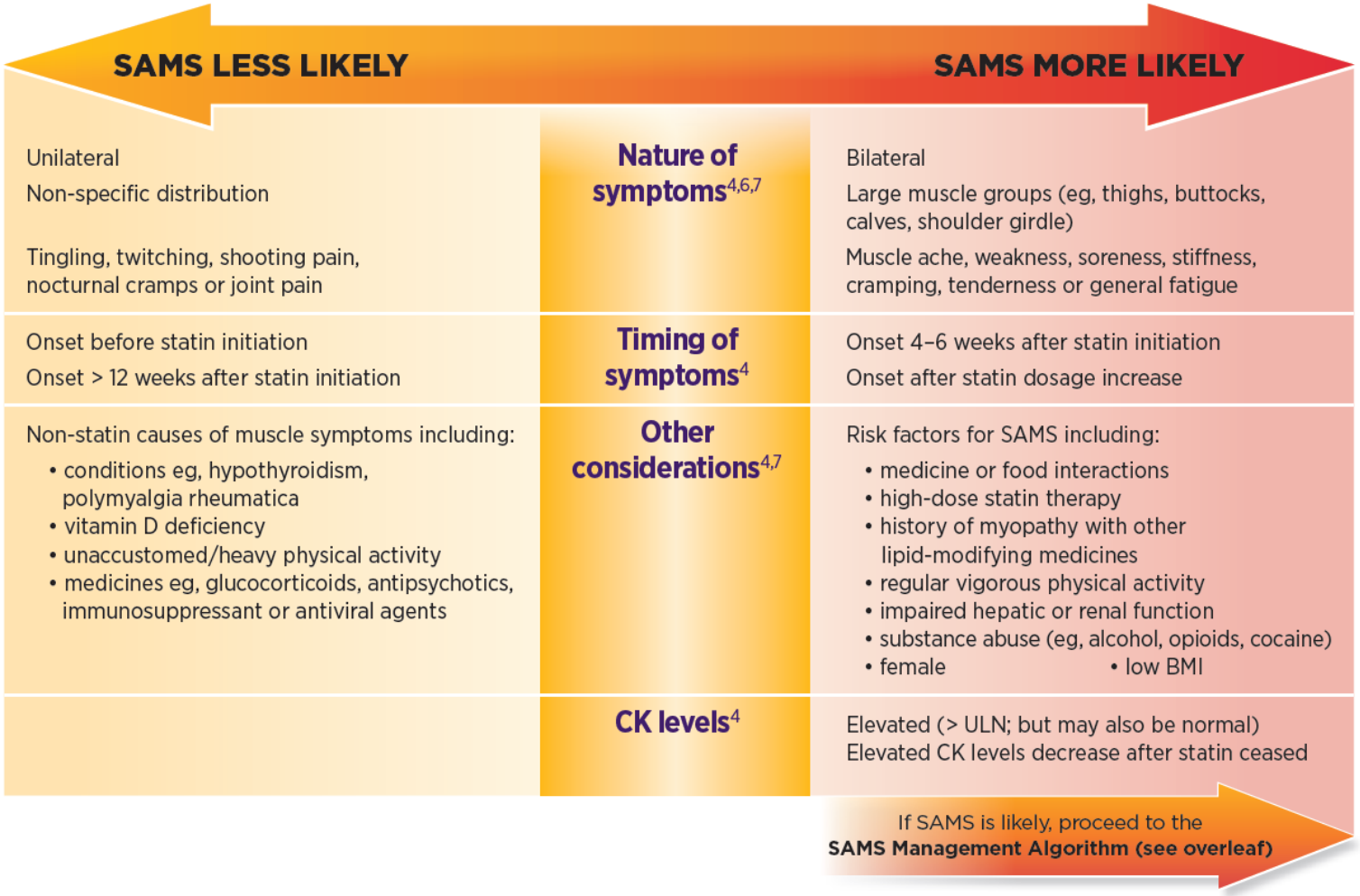
How do you know if statins are the culprit?

SAMS Assessment Guide



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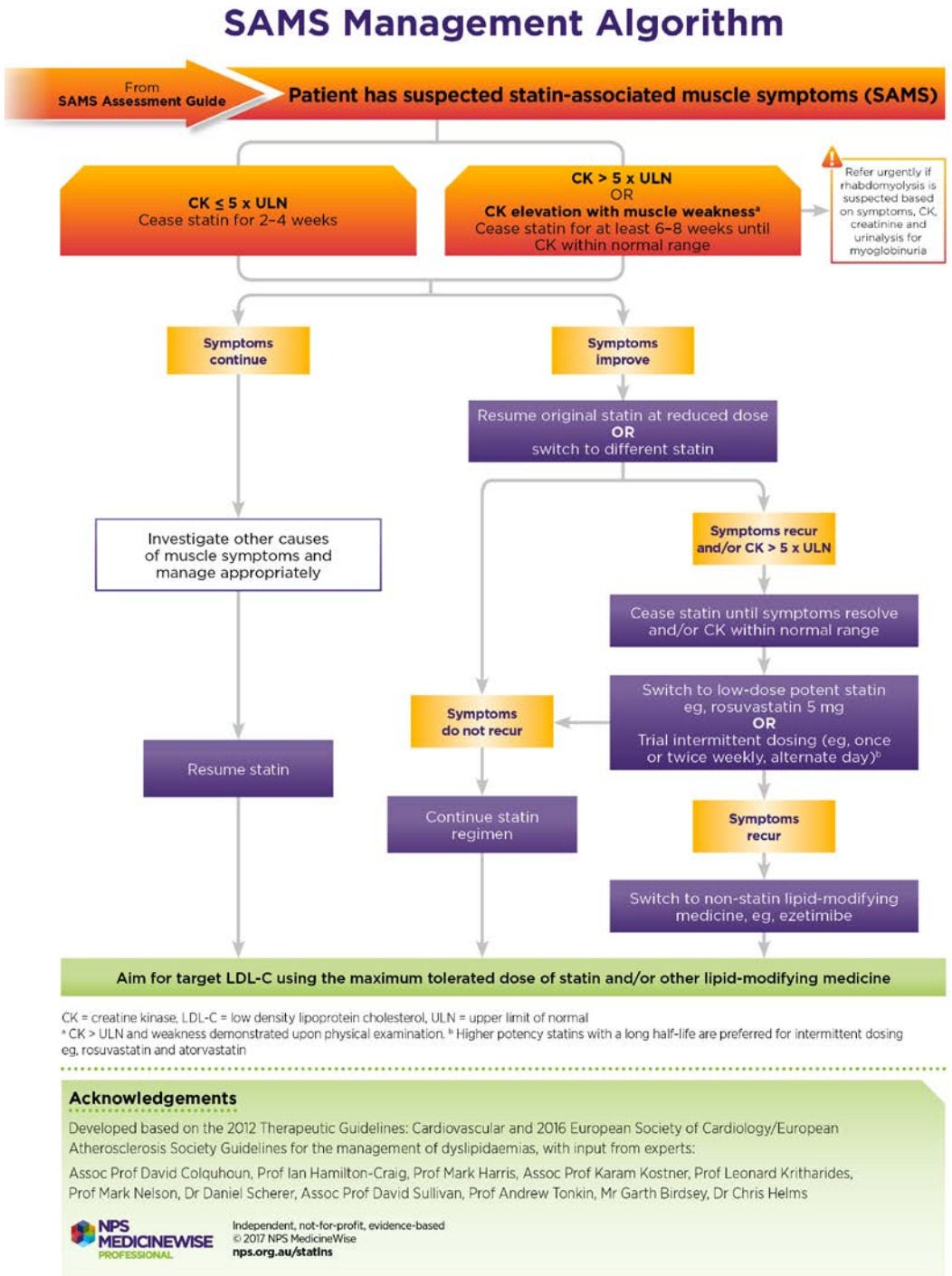
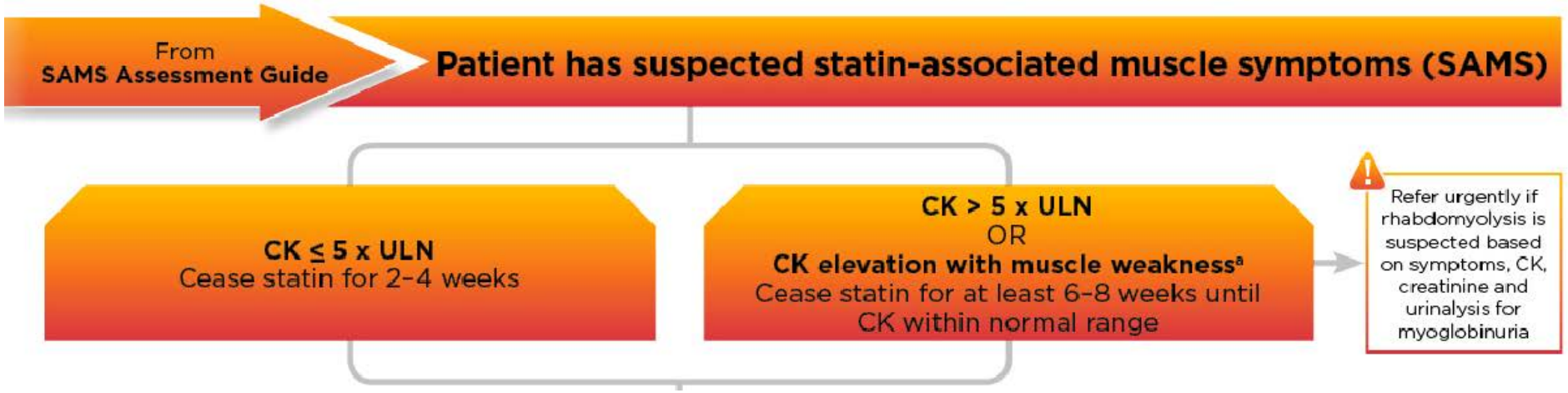
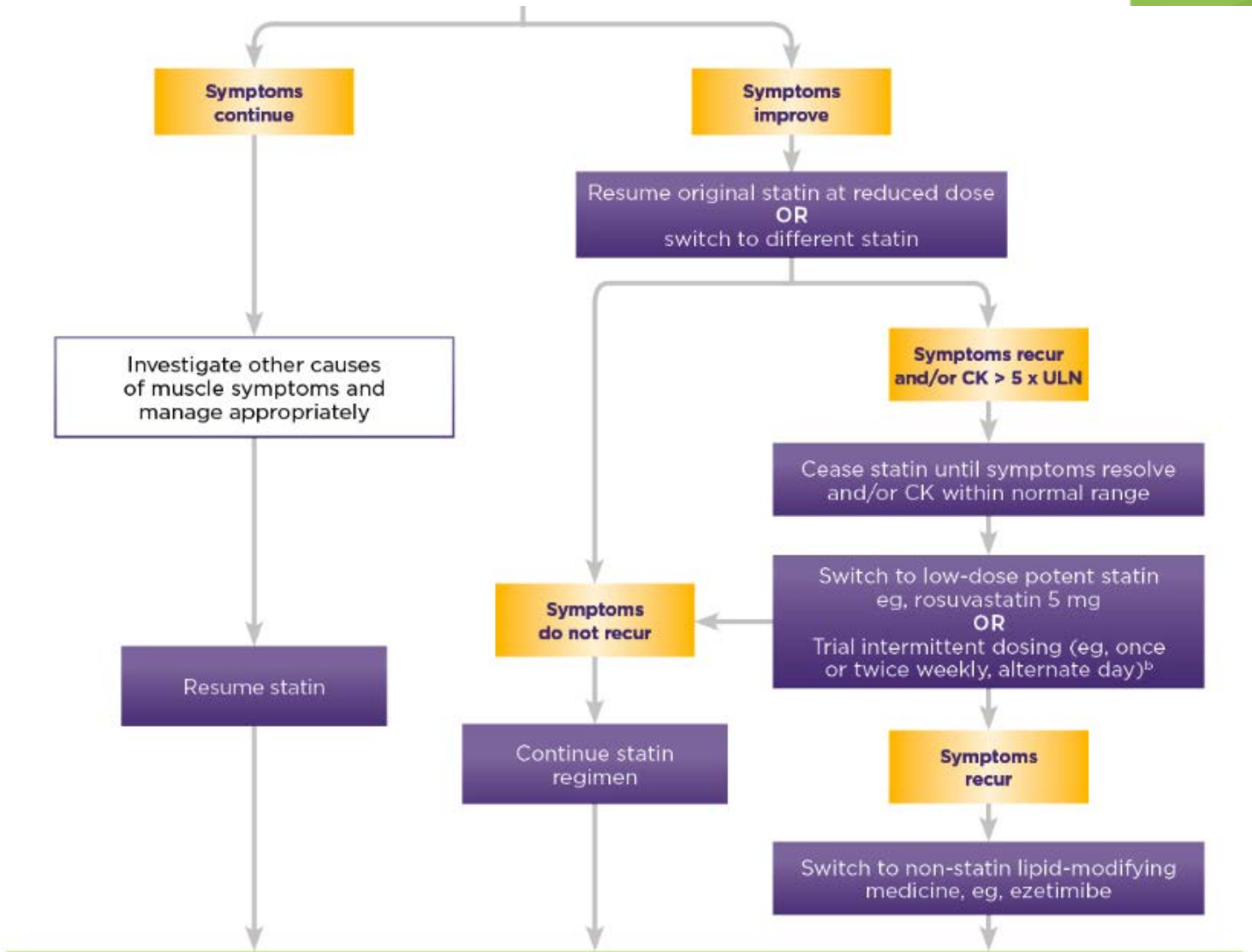
Managing SAMS – first Australian management algorithm



SAMS Management Algorithm





CK = creatine kinase, LDL-C = low density lipoprotein cholesterol, ULN = upper limit of normal
[a] CK > ULN and weakness demonstrated upon physical examination. [b] 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

Questions?

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