2023/05/18

Efficacy and safety of the alternate-day versus daily dosing of statins

報告：盧芷芸 藥師
指導：彭筠婷 藥師

OUTLINE

第 1 部分

临床情境

01 臨床情境

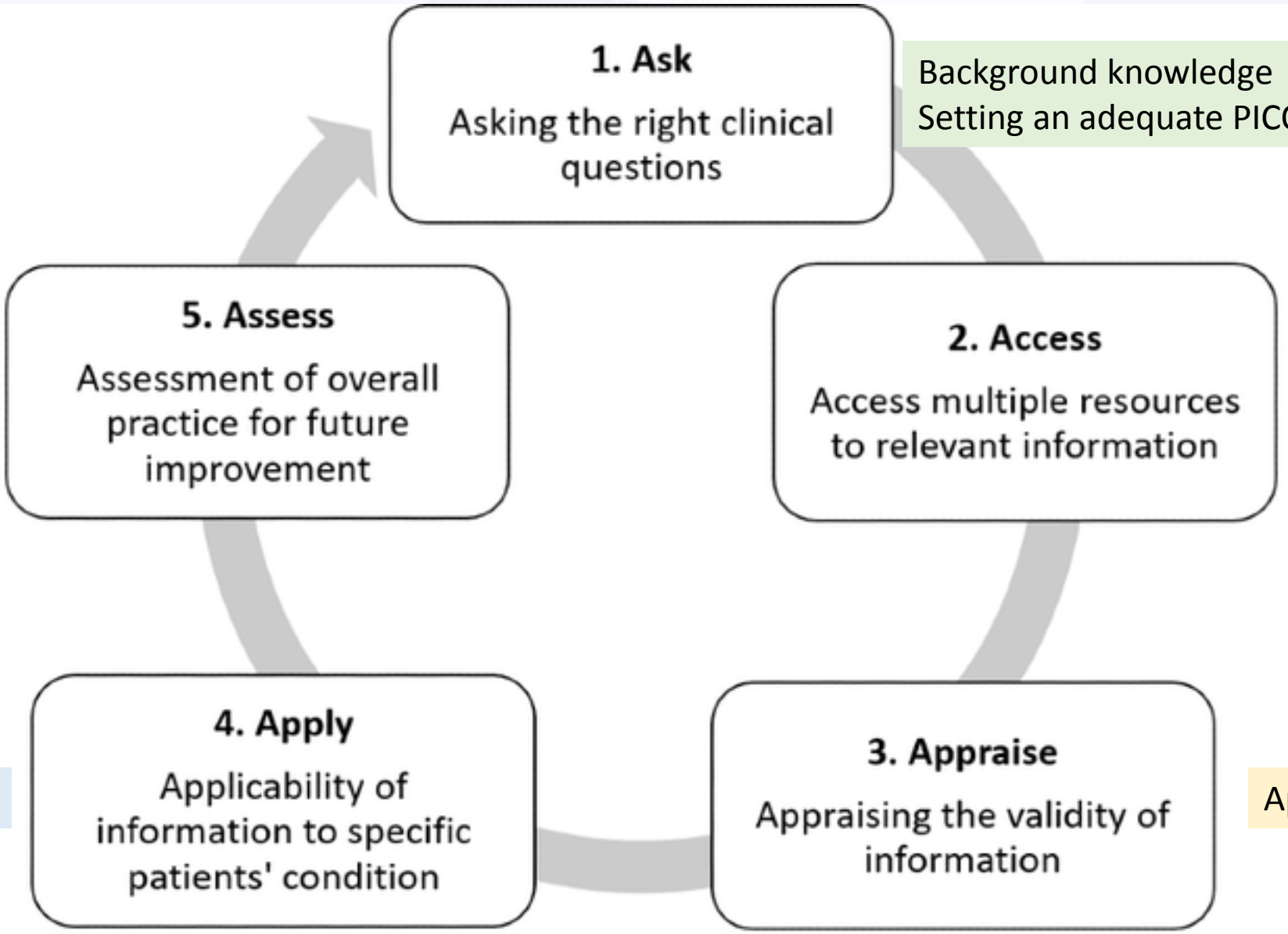
84歲姜先生，罹患有第二型糖尿病、糖尿病腎病變、高血壓、混合型高血脂，回診向醫師抱怨有肌肉疼痛的問題，故本次回診醫師將藥品調整如下：

藥品名稱	劑量	頻次	途徑
Semaglutide injection-4mg/vial	1 mg	QW	Subcutaneous
Glimepiride-2mg	0.5 tablet	QDAC	Oral
Pioglitazone-30 mg	1 tablet	QD	Oral
Rosuvastatin-10mg	1 tablets	QOD	Oral
Pentoxifylline-400 mg	1 tablet	BID	Oral

姜先生對於降膽固醇藥物的用法有疑問，想請教諮詢藥師如何服用，藥師致電處方醫師確認後，醫師表示原本是每日規律用藥，但因為姜先生抱怨肌肉疼痛，故調整藥品劑量，希望病人每兩天服用一次。

醫師調整rosuvastatin的給藥方法，是否能維持相同的降血脂效果？是否能減少藥物的不良反應？諮詢藥師應如何衛教姜先生？

01 临床情境



Background knowledge
Setting an adequate PICO

Searching strategy

Appraisal (CASP)

Back to our patient

第 2 部分

Background

Introduction

- Cardiovascular (CV) disease, including atherosclerotic cardiovascular disease (ASCVD), is one of the major leading causes of death in Taiwan.
- The causal link of LDL-C and ASCVD was further proved in many clinical trials showing that intensive reduction of LDL-C is an effective therapy to attenuate the progression of coronary atherosclerosis and improve CV outcomes.
- However, the control rate of LDL-C is disappointing in Taiwan. Even in patients with ASCVD, only 54% of them could achieve an LDL-C level <100 mg/dL.

- Recommendation :

1. Clinically significant ASCVD needs immediate and intensive reduction of LDL-C.
2. For primary prevention in subjects without clinically significant ASCVD, risk stratification is necessary to determine the lipid lowering strategy.

2022 Taiwan lipid guidelines for primary prevention. *Journal of the Formosan Medical Association = Taiwan yi zhi*, *121*(12), 2393 – 2407

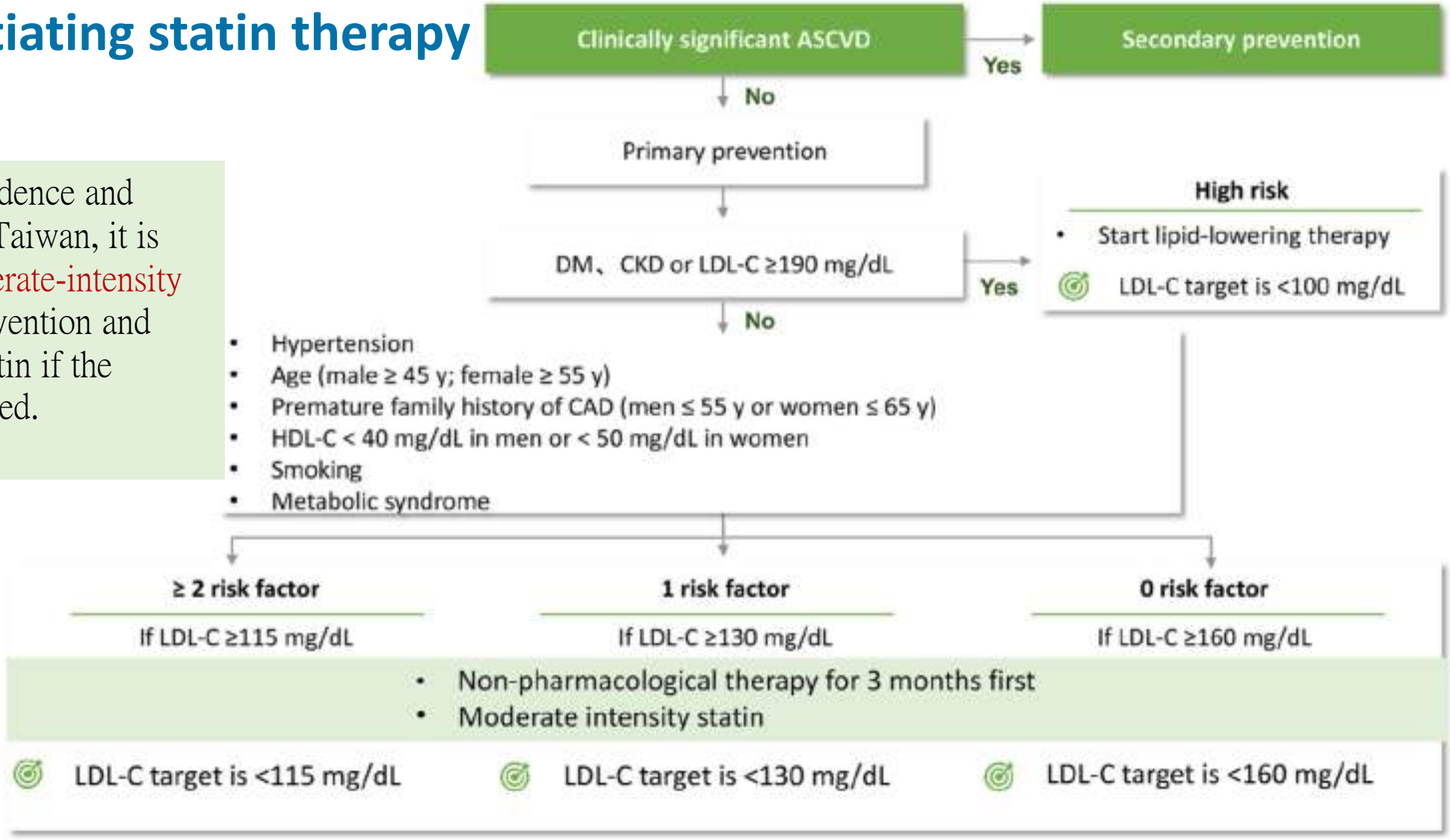
Lipid profile goal

LDL-C	Desirable	<100 mg/dl	TG	Desirable	<150 mg/dl
	Acceptable	100-129		Borderline high	150-199
	Borderline high	130-159		High	200-499
	High	160-189		Very high	≥500
	Very high	≥190			
HDL-C	Desirable	>60	TC	desirable	<200
	Acceptable	40-60		Borderline high	200-239
	Low	<40		High	≥240

2022 Taiwan lipid guidelines for primary prevention. *Journal of the Formosan Medical Association = Taiwan yi zhi*, *121*(12), 2393 – 2407

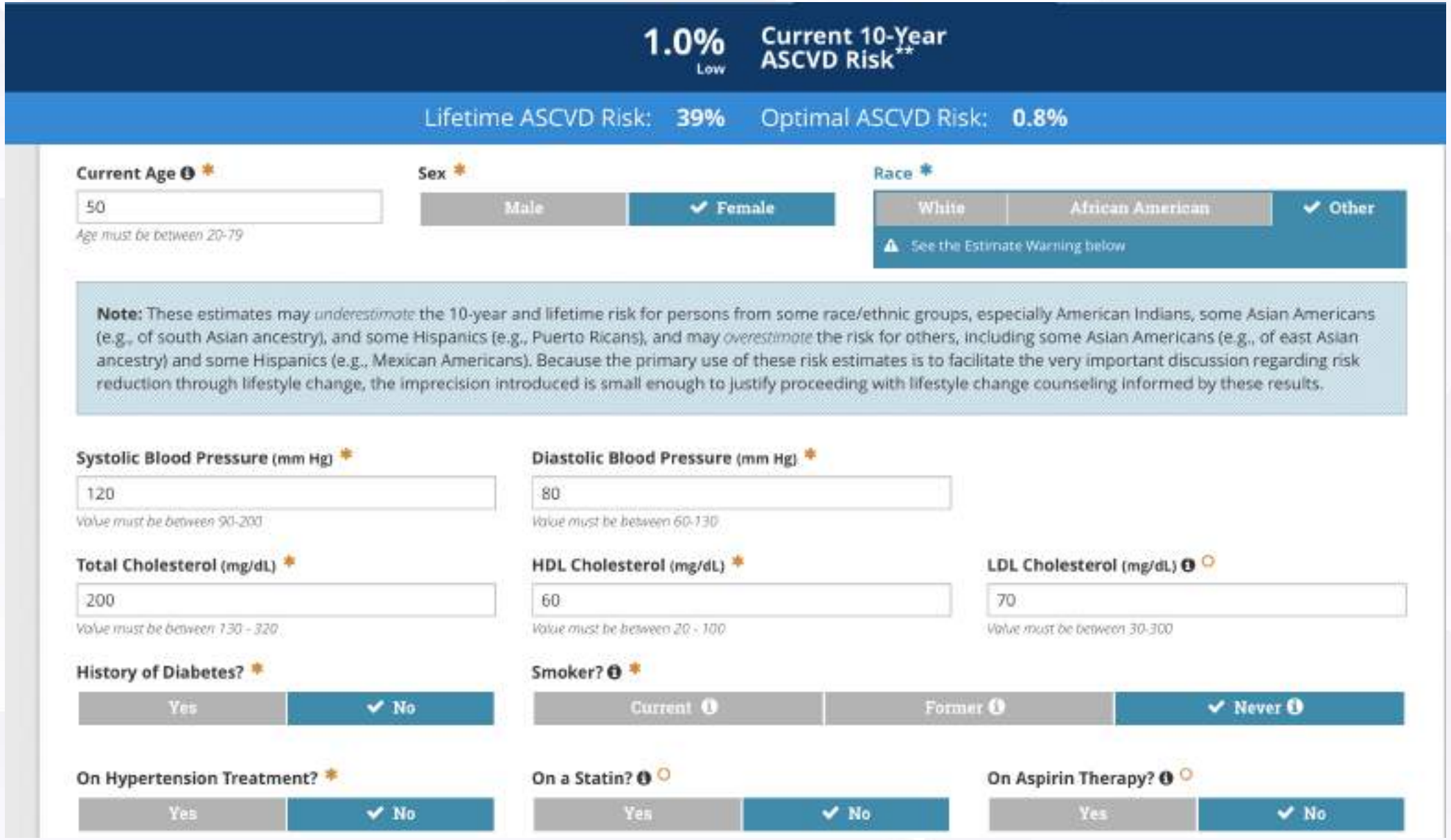
Timing for initiating statin therapy

Based on the scientific evidence and baseline LDL-C levels in Taiwan, it is reasonable to initiate moderate-intensity statin first for primary prevention and titrate to high-intensity statin if the treatment goal is not reached.



2022 Taiwan lipid guidelines for primary prevention. *Journal of the Formosan Medical Association = Taiwan yi zhi, 121*(12), 2393 – 2407

02 Background



Comparison of Statins

Statin	High-intensity	Moderate-intensity	Low-intensity	本院品項
Rosuvastatin	20-40 mg	5-10mg		Crestor 10mg
Atorvastatin	40-80mg	10-20mg		Tulip 20mg
Simvastatin		20-40mg	10mg	Simvahexal 20mg
Pravastatin		40-80mg	10-20mg	-
Lovastatin		40mg	20mg	Linicor 20mg
Fluvastatin		80mg	20-40mg	-
Pravastatin		2-4mg	1mg	-

Statins-associated muscle symptoms

- **Myopathy(肌肉病變):**
  Muscle weakness (not due to pain), with or without an elevation in CK level.
- **Myalgia(肌肉痛):**
  A symptom of muscle-discomfort, including muscle aches, soreness, stiffness, tenderness, or cramps with or soon after exercise, with a normal creatine kinase (CK) level.
- **Myositis(肌炎):**
  Defined as muscle inflammation.
- **Myonecrosis(肌肉壞死):**
  Elevation in muscle enzymes compared with either baseline CK levels (while not on statin therapy) or the upper limit of normal.
- **Clinical rhabdomyolysis(橫紋肌溶解症):**
  Myonecrosis with myoglobinuria or acute renal failure (an increase in serum creatinine of at least 0.5 mg/dL

Statins-associated muscle symptoms

Symptoms:

Proximal, symmetric muscle weakness and/or soreness

The onset of muscle symptoms is usually within weeks to months after the initiation of statin therapy but may occur at any time during treatment.

Risk factor:

- Statin characteristic: lovastatin, atorvastatin, simvastatin (metabolized by CYP3A4), rosuvastatin
- Statin dosage
- Preexisting neuromuscular disorders
- Hypothyroidism, hypovitaminosis D
- Genetic factor
- Concurrent drug therapy(e.g. CYP 3A4 inhibitor, fibrates)
- Exercise

Statins-associated muscle symptoms

Diagnosis:

The diagnosis of symptomatic and more severe myositis and myonecrosis with laboratory abnormalities (ie, increased serum creatine kinase [CK]) is typically straightforward and based on a temporal association for both onset with initiation of statin therapy and resolution with statin withdrawal.

Myalgias and weakness usually resolve and serum CK concentrations return to normal over days to weeks after discontinuation of the drug.

However, **many patients can have muscle symptoms from statin therapy without an elevation in serum CK.**

02 Background

Regarding this statin regimen:

		Enter score:
A. Location and pattern of muscle symptoms *(if more than one category applies, record the highest number)*		
Symmetric, hip flexors or thighs	3	
Symmetric, calves	2	
Symmetric, proximal upper extremity	2	
Asymmetric, intermittent, or not specific to any area	1	
B. Timing of muscle symptom onset in relation to starting statin regimen		
<4 weeks	3	
4 to 12 weeks	2	
>12 weeks	1	
C. Timing of muscle symptom improvement after withdrawal of statin *(if patient is still taking statin, stop regimen and monitor symptoms)*		
<2 weeks	2	
2 to 4 weeks	1	
No improvement after 4 weeks	0	

Rechallenge the patient with a statin regimen,
(even if same statin compound or regimen as above)
then complete final question:

D. Timing of recurrence of similar muscle symptoms in relation to starting second regimen		
<4 weeks	3	
4 to 12 weeks	1	
>12 weeks or similar symptoms did not reoccur	0	
Total: All four scores above must be entered before totaling		

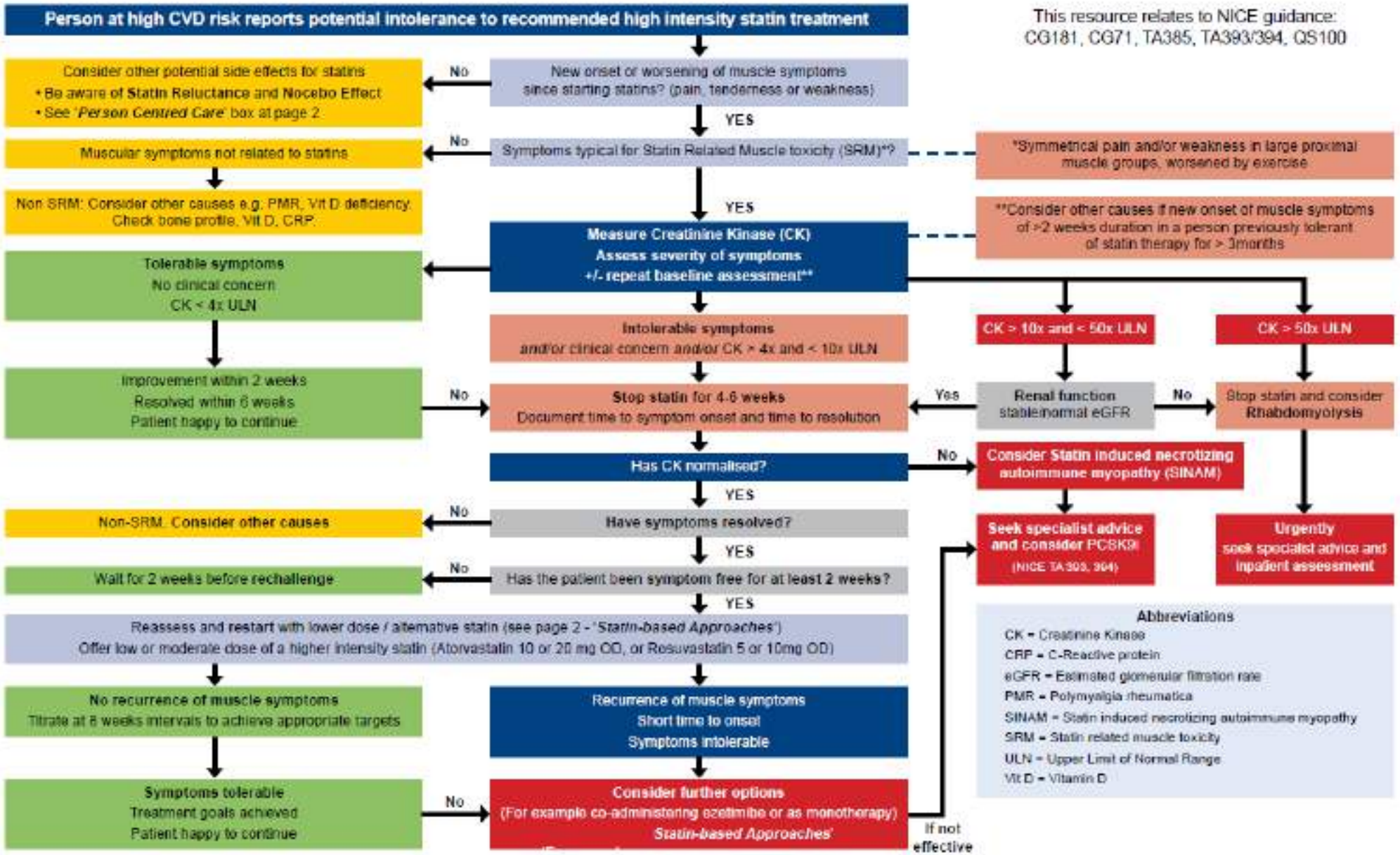
Total score	2 to 4	5 to 8	9 to 11
Likelihood that the patient's muscle symptoms are due to statin use	unlikely	possible	probable

Statin Intolerance Pathway

ACCELERATED ACCESS COLLABORATIVE

NHS England

This resource relates to NICE guidance:
CG181, CG71, TA385, TA393/394, QS100



第 3 部分

PICO&搜尋策略

03 PICO&搜尋策略

Question	Step 1 (Level 1*)	Step 2 (Level 2*)	Step 3 (Level 3*)	Step 4 (Level 4*)	Step 5 (Level 5)
How common is the problem?	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances**	Local non-random sample**	Case-series**	n/a
Is this diagnostic or monitoring test accurate? (Diagnosis)	Systematic review of cross sectional studies with consistently applied reference standard and blinding	Individual cross sectional studies with consistently applied reference standard and blinding	Non-consecutive studies, or studies without consistently applied reference standards**	Case-control studies, or "poor or non-independent reference standard**	Mechanism-based reasoning
What will happen if we do not add a therapy?	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomized trial*	Case-series or case-control studies, or poor quality prognostic cohort	n/a
Does this intervention help? (Treatment Benefits)	Systematic review of randomized trials or *n*-of-1 trials	Randomized trial or observational study with dramatic effect	Non-randomized controlled cohort/follow-up study**	Case-series, case-control studies, or historically controlled studies**	Mechanism-based reasoning
COMMON harms? (Treatment Harms)	trials, systematic review of nested case-control studies, *n*-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	or (exceptionally) observational study with dramatic effect	study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)**	or historically controlled studies**	reasoning
What are the RARE harms? (Treatment Harms)	Systematic review of randomized trials or *n*-of-1 trial	Randomized trial or (exceptionally) observational study with dramatic effect			
Is this (early detection) test worthwhile? (Screening)	Systematic review of randomized trials	Randomized trial	Non -randomized controlled cohort/follow-up study**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning

03 PICO&搜尋策略

若使用hyperlipidemia等關鍵字無法搜出適用文章，於是改用lipid等關鍵字

	關於此病人	轉換關鍵字
P	Mixed-hyperlipidemia	Lipid or cholesterol or low-density-lipoprotein cholesterol
I	Rosuvastatin QOD	Hydroxymethylglutaryl coenzyme a reductase inhibitor AND alternate day
C	Daily dosing rosuvastatin	Daily dosing
O	Efficacy and adverse effect	Adverse event AND therapy OR Safety

Rosuvastatin的文章年代較久遠、樣本數小、outcome不完全吻合，故將關鍵字改為HMG coA reductase inhibitor

03 PICO&搜尋策略

Embase

Embase

Population e.g. diabetes

lipid /exp | 5 synonyms :all | OR

low density lipoprotein cholesterol /exp | 4 synonyms :all | OR

cholesterol /exp | 13 synonyms :all

Intervention e.g. insulin

hydroxymethylglutaryl coenzyme A reductase inhibitor /exp | 9 synonyms :all | AND

alternate day :all

Comparison e.g. placebo

daily dosing :all

Outcome e.g. risk

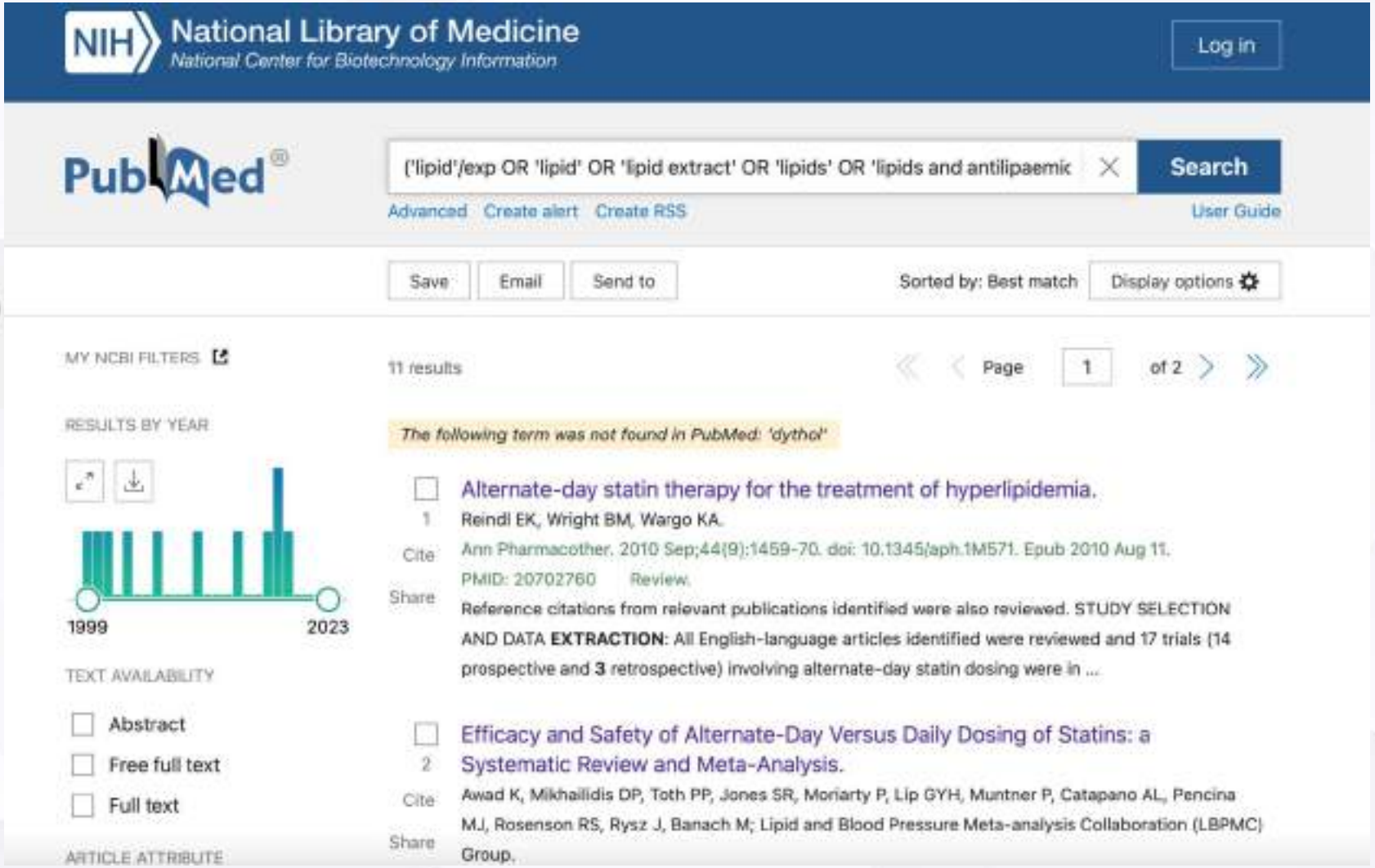
therapy /exp | 23 synonyms :all | AND | adverse event /exp | 5 synonyms :all

OR | safety /exp | 5 synonyms :all

Show 8 results

03PICO&搜尋策略

Pubmed



Cochrane

Cochrane Library
Trusted evidence.
Informed decisions.
Better health.

−	+	#1	MeSH descriptor: [Cholesterol] explode all trees	MeSH	11718
−	+	#2	statins	Limits	6421
−	+	#3	every-other-day	Limits	2497
−	+	#4	daily dosing	Limits	13067
−	+	#5	adverse event	Limits	49368
−	+	#6	efficacy	Limits	433130
−	+	#7	safety	Limits	296273
−	+	#8	#1 or #2	Limits	17252
−	+	#9	#3 and #4	Limits	126
−	+	#10	#5 or #6 or #7	Limits	555533
−	+	#11	#8 and #9 and #10	Limits	6

03 PICO&搜尋策略

No.	Literature	P	I	C	O
1	**Efficacy and Safety of Alternate-Day Versus Daily Dosing of Statins: a Systematic Review and Meta-Analysis** **Awad K. et al.*Cardiovascular Drugs and Therapy* 2017 31:4 (419-431)**	✓	✓	✓	✓
2	Alternate-day statin therapy for the treatment of hyperlipidemia. Reindl, E. K. et al.*The Annals of pharmacotherapy*, 2010 *44*(9), 1459–1470. 無法取得全文	✓	✓	✓	✓
3	Long-term efficacy of non-daily statin dosing in previously intolerant patients: The Atlanta va medical center experience Fayfman M. et al. *Journal of Clinical Lipidology* 2015 9:3 (460-461)	✓	✗	✓	✗
4	Alternate-day dosing with statins Marcus F.I. et al. *American Journal of Medicine* 2013 126:2 (99-104)	✓	✓	✓	✓

A review of published data(without a systematic combined results)

03 PICO&搜尋策略

No.	Literature	P	I	C	O
5	Efficacy of alternate-day versus everyday dosing of atorvastatin Pramanik S. et al.*Indian Journal of Pharmacology* 2012 44:3 (362-365)	✓	✗	✗	✓
6	Efficacy of alternate day dosing of atorvastatin Aghasadeghi K., Zare D.*Central European Journal of Medicine* 2008 3:2 (163-166)	✓	✗	✗	✓
7	Alternate-day dosing of atorvastatin: Effects in treating type 2 diabetic patients with dyslipidaemia Ferrer-García J.C et al. *Acta Diabetologica* 2006 43:3 (75-78)	✗	✗	✗	✓
8	Is alternate daily dose of atorvastatin effective in treating patients with hyperlipidemia? The Alternate Day Versus Daily Dosing of Atorvastatin Study (ADDAS) Matalka M.S. et al.*American Heart Journal* 2002 144:4 (674-677)	✓	✗	✗	✗

03 PICO&搜尋策略

No.	Literature	P	I	C	O
9	Can alternate-day Statin regimen minimize its adverse effects on muscle and tendon? A systematic review Muhammad, Z. A et al. *JPMA. The Journal of the Pakistan Medical Association*, *69*(7), 1006–1013.	✓	✓	✓	✗
10	Alternate-day dosing of HMG- CoA reductase inhibitors for cholesterol reduction. Metz CA, Lucas KH. Ann Pharmacother. 2001 Apr;35(4):496-500.	✓	✗	✗	✓

年代久遠、未收錄rosuvastatin

Cardiovasc Drugs Ther (2017) 31:419–431
DOI 10.1007/s10557-017-6743-0

REVIEW ARTICLE

Efficacy and Safety of Alternate-Day Versus Daily Dosing of Statins: a Systematic Review and Meta-Analysis

Kamal Awad[1] · Dimitri P. Mikhailidis[2] · Peter P. Toth[3,4] · Steven R. Jones[4] · Patrick Moriarty[5,6] · Gregory Y. H. Lip[7] · Paul Muntner[8] · Alberico L. Catapano[9,10] · Michael J. Pencina[11] · Robert S. Rosenson[12] · Jacek Rysz[13] · Maciej Banach[13,14,15] · on behalf of the Lipid and Blood Pressure Meta-analysis Collaboration (LBPMC) Group

第 4 部分

CASP Appraisal

04 CASP Appraisal

1. Did the review address a c

P	Not specified?
I	Alternate-day statin
C	Daily dosing statin
O	Efficacy and safety

Population
Patients with hypercholesterolemia
Patients with hypercholesterolemia
Naïve patients of dyslipidemia
Patients who were receiving pravastatin daily and had maintained their NCEP-defined LDL-C goal for at least 3 months
Patients with type 2 DM with hypercholesterolemia
Patients with LDL-C of 100 to 200 mg/dL
Patients with serum TC levels >200 mg/dL and LDL-C levels >130 mg/dL
Patients with LDL-C ≥160 mg/dL and/or TG ≥200 mg/dL
Patients who were receiving atorvastatin for at least 6 months and had met their NCEP-defined LDL-C goal
Patients with hypercholesterolemia
Patients with CAD
Patients with a LDL-C level >160 mg/dL despite at least 3 months of a low-fat diet
Patients with hypercholesterolemia

Yes	
Can't Tell	
No	

Purpose W
trolled trial
about the e
of statins.

nized con-
e evidence
aily dosing

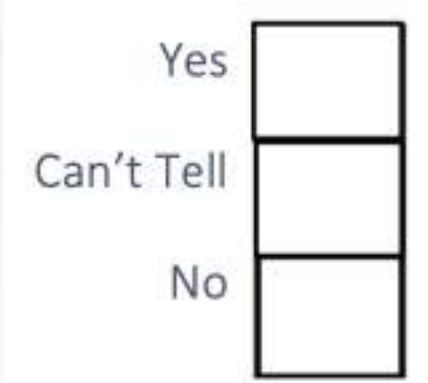
2.Did the authors look for the right type of papers?

Yes ☐
Can't Tell ☐
No ☐

Table 1 Summary of the included studies

Study	Year	Location	Design	Duration	Statin used (doses)	Population
Aghasadeghi et al.	2008	Iran	Randomized, blinded, controlled, parallel trial	6 weeks	Atorvastatin (20 mg QOD vs 20 mg QD)	Patients with hypercholesterolemia
Dulay et al.	2009	Canada	Quasi-randomized, open-label, controlled, crossover trial	6 weeks then 4 weeks washout period and another 6 weeks	Rosuvastatin (20 mg QOD vs 10 mg QD)	Patients with hypercholesterolemia
Ghia et al.	2014	India	Randomized, open-label, controlled, parallel trial	3 months	Atorvastatin (10 mg QOD vs 10 mg QD)	Naïve patients of dyslipidemia
Graham et al.	2002	USA	Randomized, open-label, controlled, parallel trial	4 months	Pravastatin (same dose QOD vs half dose as before QD)	Patients who were receiving pravastatin daily and had maintained their NCEP-defined LDL-C goal for at least 3 months
Hadjibabaie et al.	2007	Iran	Randomized, open-label, controlled, parallel trial	8 weeks	Atorvastatin (10 mg QOD vs 10 mg QD)	Patients with type 2 DM with hypercholesterolemia
Jafari et al.	2003	USA	Randomized, open-label, controlled, parallel trial	6 weeks	Atorvastatin (10 mg QOD vs 10 mg QD)	Patients with LDL-C of 100 to 200 mg/dL
Keles et al.	2008	Turkey	Randomized, controlled, parallel trial	3 months	Atorvastatin (20 mg QOD vs 20 mg QD)	Patients with serum TC levels >200 mg/dL and LDL-C levels >130 mg/dL
Li et al.	2012	China	Randomized, controlled, parallel trial	6 weeks	Rosuvastatin (10 mg QOD vs 10 mg QD)	Patients with LDL-C ≥160 mg/dL and/or TG ≥200 mg/dL
Pattanaik et al.	2012	India	Randomized, open-label, controlled, parallel trial	12 weeks	Atorvastatin (same dose as before QOD vs same dose as before QD)	Patients who were receiving atorvastatin for at least 6 months and had met their NCEP-defined LDL-C goal
Pramanik et al.	2012	India	Randomized, open-label, controlled, crossover trial	12 weeks then 4 weeks washout period and another 12 weeks	Atorvastatin (20 mg QOD vs 20 mg QD)	Patients with hypercholesterolemia
Rifaie et al.	2012	Egypt	Randomized, single-blinded, controlled, parallel trial	6 weeks	Atorvastatin (10 mg QOD vs 10 mg QD)	Patients with CAD
Rindone et al.	1998	USA	Randomized, open-label, controlled, crossover trial	6 weeks for each regime	Fluvastatin (40 mg QOD vs 20 mg QD)	Patients with a LDL-C level >160 mg/dL despite at least 3 months of a low-fat diet
Wongwiwatthananukit et al.	2006	Thailand	Randomized, open-label, controlled, parallel trial	8 weeks	Rosuvastatin (10 mg QOD vs 10 mg QD)	Patients with hypercholesterolemia

3. Do you think all the important, relevant studies were included?



We performed a computerized literature search of PubMed, SCOPUS, Web of Science, and Embase from inception until January 2, 2017 using the following keywords: (atorvastatin OR fluvastatin OR lovastatin OR pitavastatin OR pravastatin OR rosuvastatin OR simvastatin OR cerivastatin OR mevinolin OR statin OR statins) and (alternate day OR alternate-day OR every other day OR every-other-day OR non-every day OR non-daily OR twice a week OR twice-weekly OR twice weekly OR once a week OR once-weekly OR once weekly). To ensure that no relevant studies were missed, we conducted manual searches for potential trials that were included in the reference lists of review articles on that topic and the abstracts from selected congresses: scientific sessions of the European Society of Cardiology (ESC), the American Heart Association (AHA), American College of Cardiology (ACC), European Society of Atherosclerosis (EAS), and National Lipid Association (NLA). The wild-card term "*" was used to increase the sensitivity of the search strategy. The literature search was restricted to articles published in English and conducted on human subjects.

After removal of duplicate articles by Endnote X7 (Thompson Reuter, CA, USA), two independent authors screened the retrieved articles in two steps: the first step was to screen the titles and abstracts for eligibility, and the second step was to screen the full text of the eligible abstracts according to the inclusion and exclusion criteria. Disagreement was resolved by the opinion of a third author (MB).

3. Do you think all the important, relevant studies were included?

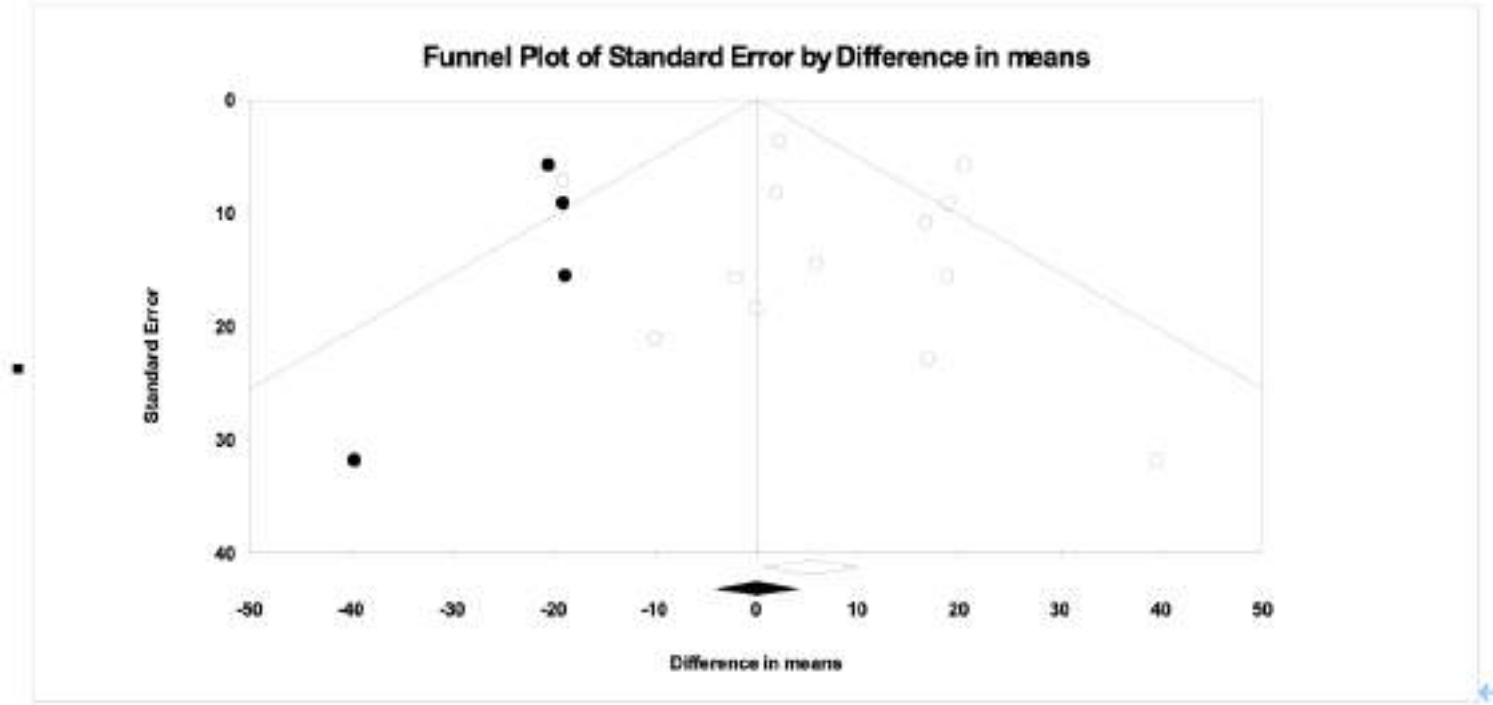


Figure S4: Shows a funnel plot displaying publication bias in the studies that compared the effects of alternate-day dosing versus daily dosing of statins on TG

Yes ☐

Can't Tell ☐

No ☐

Visual inception of funnel plots suggested a potential publication bias for TG. The trim and fill approach corrected the asymmetry of the funnel plot of TG by imputing 4 studies (corrected MD 0.28354 mg/dL, 95%CI −8.51685, 9.08393).

3. Do you think all the important, relevant studies were included?

Yes

Can't Tell

No

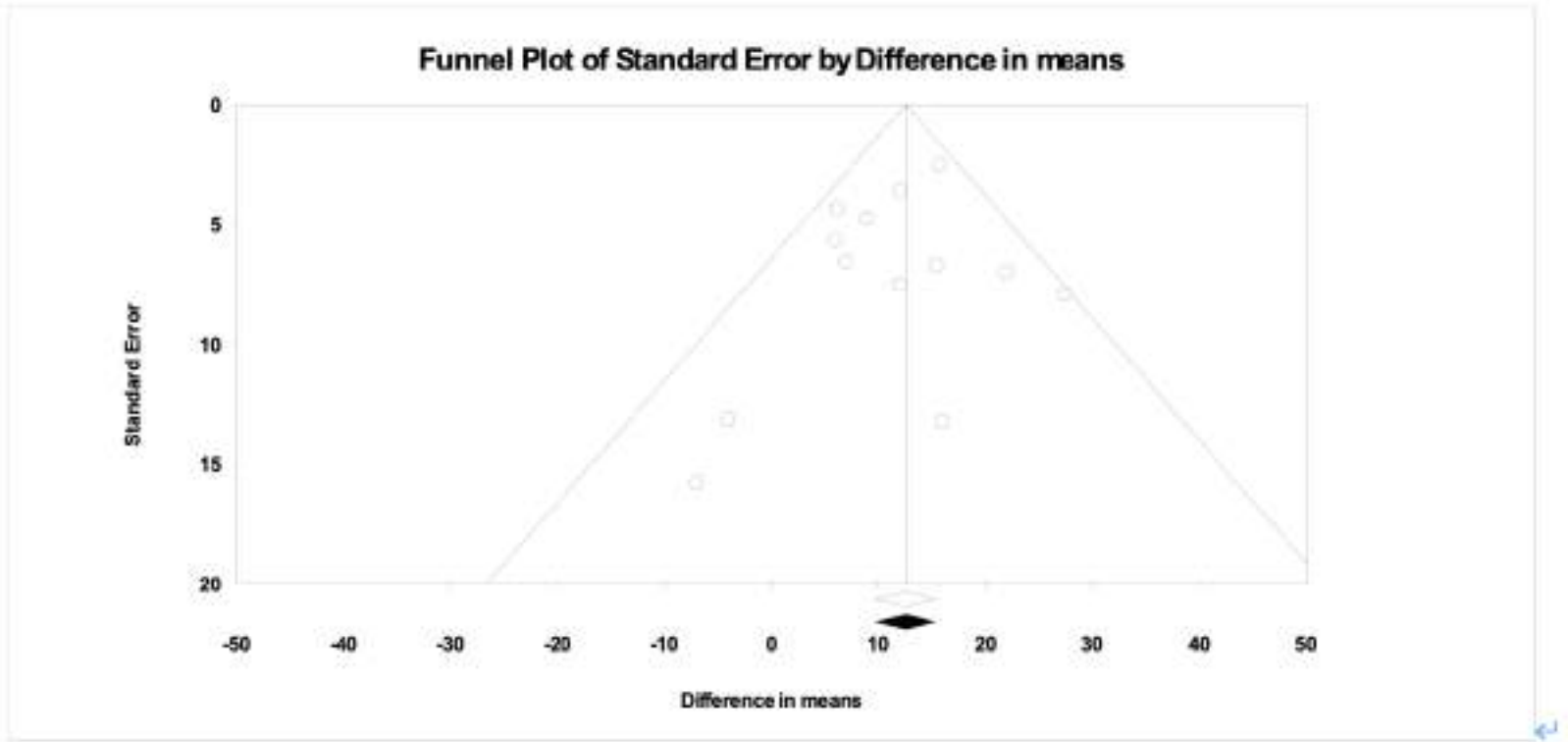


Figure S5: Shows a funnel plot displaying publication bias in the studies that compared the effects of alternate-day dosing versus daily dosing of statins on TC

3. Do you think all the important, relevant studies were included?

Yes

Can't Tell

No

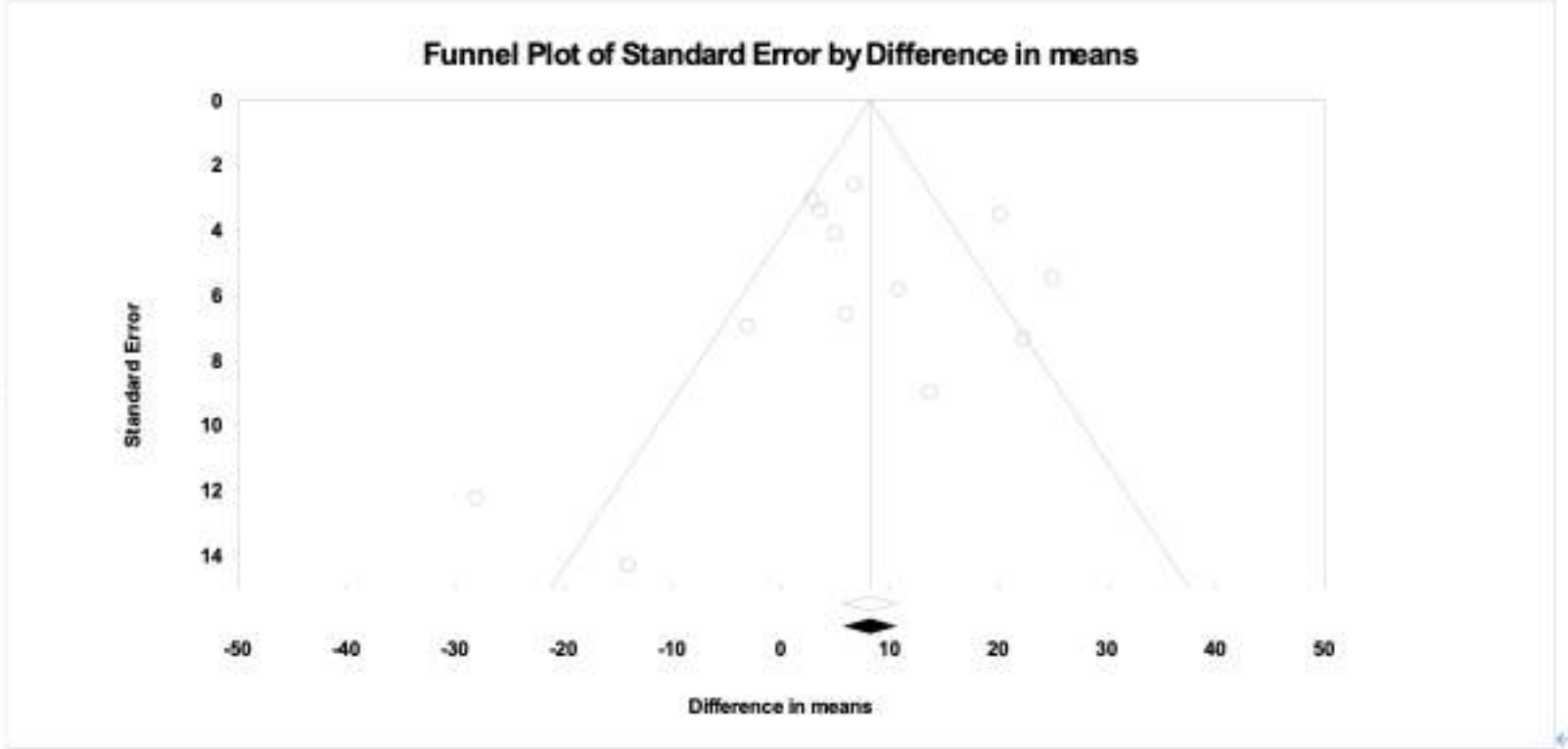
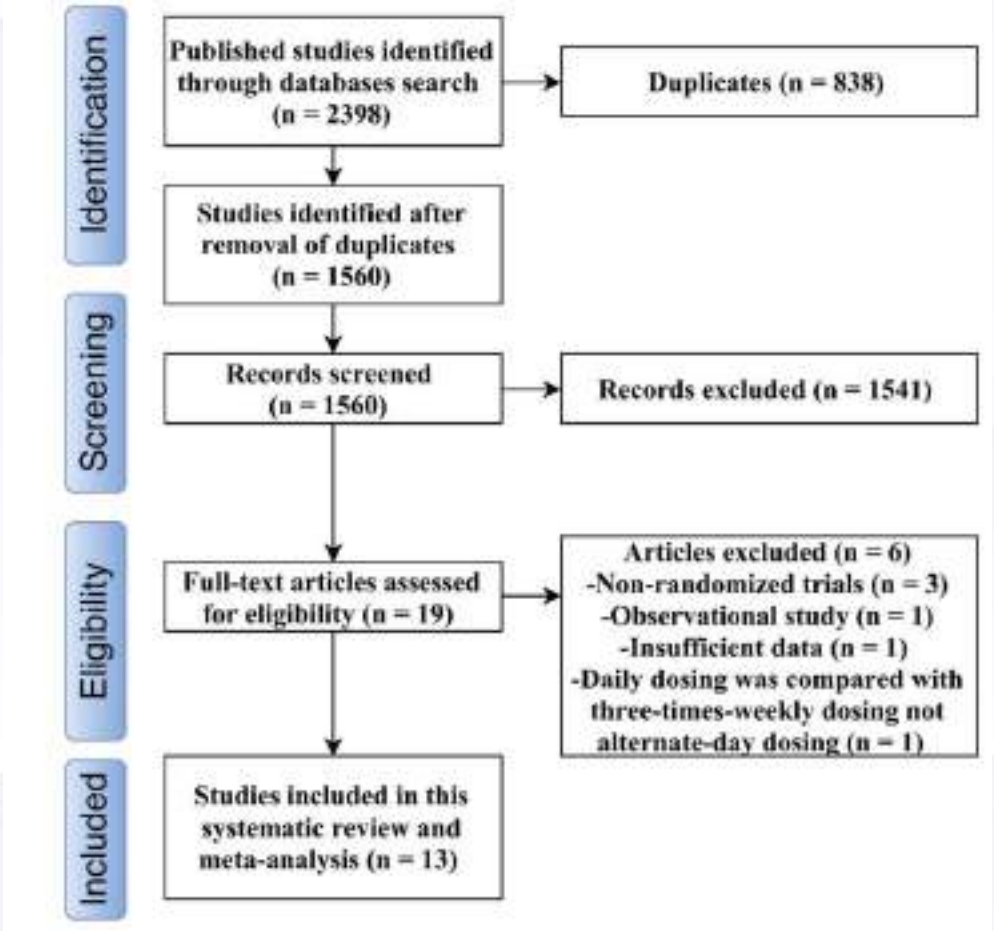
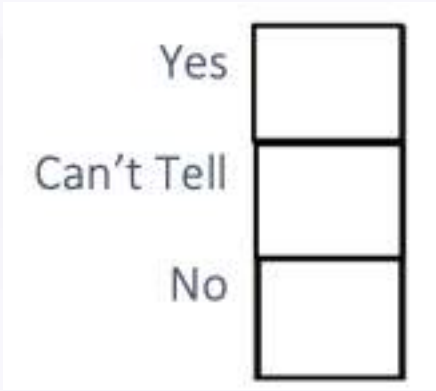


Figure S6: Shows a funnel plot displaying publication bias in the studies that compared the effects of alternate-day dosing versus daily dosing of statins on LDL-C

3. Do you think all the important, relevant studies were included?





- 有從reference去搜尋可能遺漏的文獻
- 僅收錄英文文獻
- 無收錄未發表的或去聯絡專家學者
- Funnel plot 呈現publication bias
- 無使用MeSH terms

4. Did the review's authors do enough to assess quality of the included studies?

Yes

Can't Tell

No

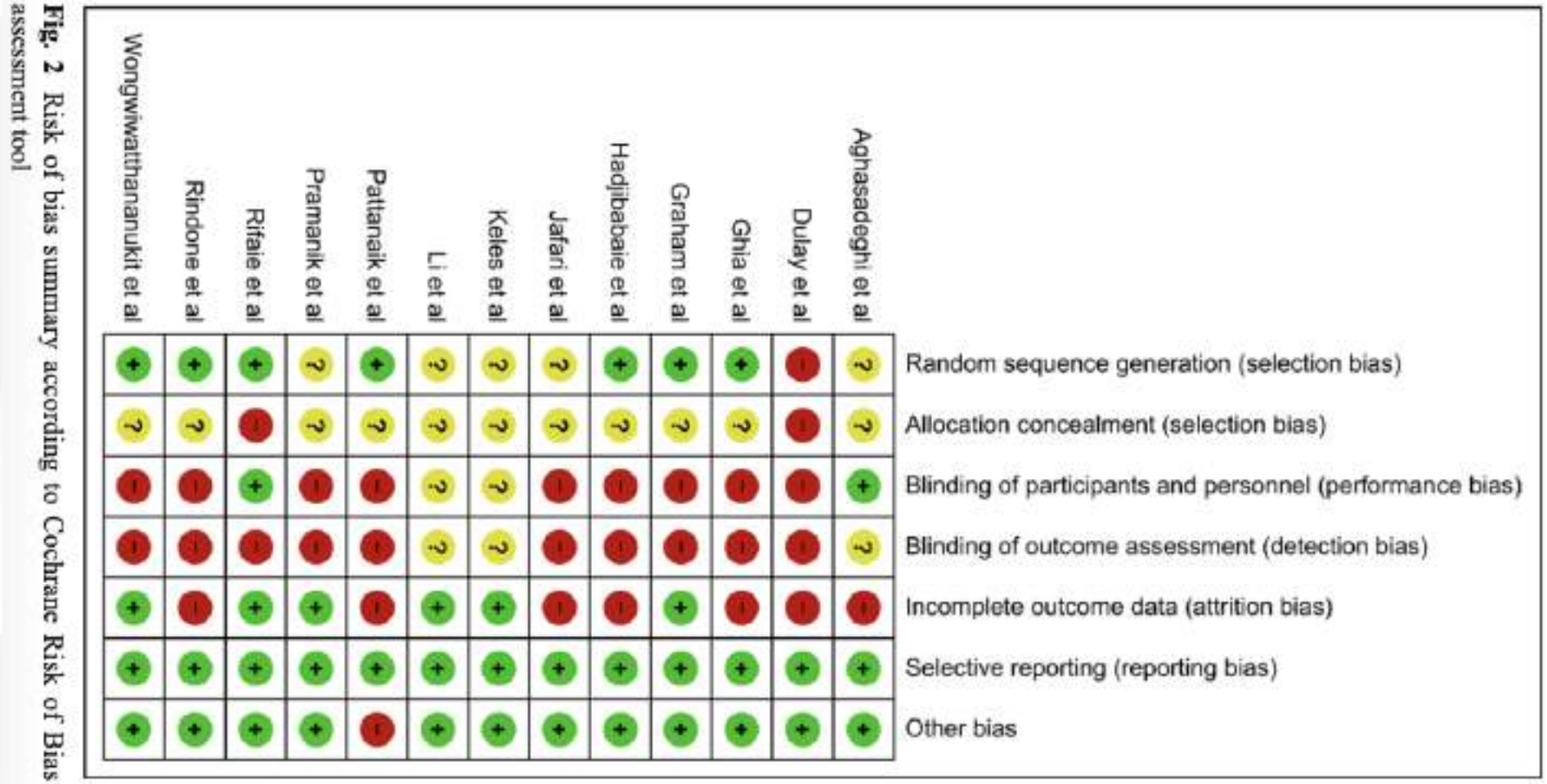


Fig. 2 Risk of bias summary according to Cochrane Risk of Bias assessment tool

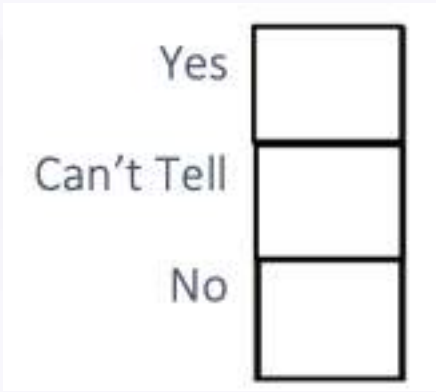
04 CASP Appraisal

Study	Year	Group (no. of patients)	Age (years)	Weight (kg)	Gender		TC (mg/dL)	LDL-C (mg/dL)	TG (mg/dL)
					M	F			
Aghasadeghi et al.	2008	Atorvastatin QOD [$n = 20$]	61 (11)	70 (8)	11	9	228 (31)	152 (31)	189 (46)
		Atorvastatin QD [$n = 20$]	55 (12)	72 (13)	10	10	226 (55)	152 (50)	176 (85)
Dulay et al.	2009	Rosuvastatin QOD [$n = 39$] Rosuvastatin QD [$n = 39$]	68.2 (12.3)	NS	24	15	232 (34.8)	147 (31)	151 (80)
Ghia et al.	2014	Atorvastatin QOD [$n = 39$]	48.13 (9.671)	62.9744 (8.7494)	18	21	246.15 (37.89)	176.05 (35.12)	135.25 (62.51)
		Atorvastatin QD [$n = 46$]	48 (8)	66.02 (8.277)	22	24	258.48 (30.86)	190.19 (27.48)	141.15 (29.65)
Graham et al.	2002	Pravastatin QOD [$n = 53$]	63 (10)	93 (21)	53	0	172 (25)	96 (18)	178 (82)
		Pravastatin QD [$n = 51$]	68 (8)	92 (19.5)	51	0	170 (24)	92 (20)	162 (76)
Hadjibabaie et al.	2007	Atorvastatin QOD [$n = 20$]	55.45 (1.74)†	NS	11	9	239.1 (5.95)†	149.45 (4.62)†	185.2 (14.4)†
		Atorvastatin QD [$n = 20$]	53.45 (2.11)†	NS	12	8	252.2 (8.79)†	153.7 (6.95)†	239.2 (19.4)†
Jafari et al.	2003	Atorvastatin QOD [$n = 18$]	56 (11)	NS	NS	NS	240 (44)	153 (30)	179 (108)
		Atorvastatin QD [$n = 19$]	56 (10)	NS	NS	NS	228 (44)	139 (29)	178 (106)
Keles et al.	2008	Atorvastatin QOD [$n = 30$]	53 (13)	NS	18	12	244 (26)	166 (25)	163 (64)
		Atorvastatin QD [$n = 31$]	57 (11)	NS	21	10	242 (29)	162 (23)	159 (55)
Li et al.	2012	Rosuvastatin QOD [$n = 19$]	48 (6)	NS	13	6	247 (15.3)	158 (9.70	137 (25.5)
		Rosuvastatin QD [$n = 18$]	50 (8)	NS	11	7	251 (16)	160 (10.1)	141 (28.4)
Pattanaik et al.	2012	Atorvastatin QOD [$n = 141$]	50.8 (7.0)	NS	90	51	145.49 (21.75)	77.68 (17.34)	126.83 (42.85)
		Atorvastatin QD [$n = 143$]	50.3 (6.9)	NS	85	58	157.45 (31.37)	80.06 (25.14)	141.25 (52.01)
Pramanik et al.	2012	Atorvastatin QOD [$n = 38$]	52.89 (1.549)[a]	61.47 (1.783)[a]	25	13	221.4 (3.696)†	150.0 (2.616)†	152.5 (8.134)†
		Atorvastatin QD [$n = 38$]					223.2 (3.266)†	149.5 (2.837)†	160.9 (6.521)†
Rifaie et al.	2012	Atorvastatin QOD [$n = 30$]	53.9 (6.4)	NS	20	10	144 (26)	79 (19)	142 (25)
		Atorvastatin QD [$n = 30$]	55 (8.9)	NS	22	8	153 (21)	87 (16)	157 (28)
Rindone et al.	1998	Fluvastatin QOD [$n = 23$] Fluvastatin QD [$n = 23$]	64 (8)	NS	22	1	269 (22)	182 (24)	244 (62)
Wongwiwatthananukit et al.	2006	Rosuvastatin QOD [$n = 40$]	62.10 (1.57)	NS	15	25	241.52 (34.04)	170.33 (28.22)	151.30 (74.41)
		Rosuvastatin QD [$n = 40$]	57.18 (1.48)	NS	17	23	256.20 (35.47)	181.73 (34.65)	155.27 (79.44)

04 CASP Appraisal

Study	Year	Location	Design	Duration	Statin used (doses)	Population
Aghasadeghi et al.	2008	Iran	Randomized, blinded, controlled, parallel trial	6 weeks	Atorvastatin (20 mg QOD vs 20 mg QD)	Patients with hypercholesterolemia
Dulay et al.	2009	Canada	Quasi-randomized, open-label, controlled, crossover trial	6 weeks then 4 weeks washout period and another 6 weeks	Rosuvastatin (20 mg QOD vs 10 mg QD)	Patients with hypercholesterolemia
Ghia et al.	2014	India	Randomized, open-label, controlled, parallel trial	3 months	Atorvastatin (10 mg QOD vs 10 mg QD)	Naïve patients of dyslipidemia
Graham et al.	2002	USA	Randomized, open-label, controlled, parallel trial	4 months	Pravastatin (same dose QOD vs half dose as before QD)	Patients who were receiving pravastatin daily and had maintained their NCEP-defined LDL-C goal for at least 3 months
Hadjibabaie et al.	2007	Iran	Randomized, open-label, controlled, parallel trial	8 weeks	Atorvastatin (10 mg QOD vs 10 mg QD)	Patients with type 2 DM with hypercholesterolemia
Jafari et al.	2003	USA	Randomized, open-label, controlled, parallel trial	6 weeks	Atorvastatin (10 mg QOD vs 10 mg QD)	Patients with LDL-C of 100 to 200 mg/dL
Keles et al.	2008	Turkey	Randomized, controlled, parallel trial	3 months	Atorvastatin (20 mg QOD vs 20 mg QD)	Patients with serum TC levels >200 mg/dL and LDL-C levels >130 mg/dL
Li et al.	2012	China	Randomized, controlled, parallel trial	6 weeks	Rosuvastatin (10 mg QOD vs 10 mg QD)	Patients with LDL-C ≥160 mg/dL and/or TG ≥200 mg/dL
Pattanaik et al.	2012	India	Randomized, open-label, controlled, parallel trial	12 weeks	Atorvastatin (same dose as before QOD vs same dose as before QD)	Patients who were receiving atorvastatin for at least 6 months and had met their NCEP-defined LDL-C goal
Pramanik et al.	2012	India	Randomized, open-label, controlled, crossover trial	12 weeks then 4 weeks washout period and another 12 weeks	Atorvastatin (20 mg QOD vs 20 mg QD)	Patients with hypercholesterolemia
Rifaie et al.	2012	Egypt	Randomized, single-blinded, controlled, parallel trial	6 weeks	Atorvastatin (10 mg QOD vs 10 mg QD)	Patients with CAD
Rindone et al.	1998	USA	Randomized, open-label, controlled, crossover trial	6 weeks for each regime	Fluvastatin (40 mg QOD vs 20 mg QD)	Patients with a LDL-C level >160 mg/dL despite at least 3 months of a low-fat diet
Wongwiwatthananukit et al.	2006	Thailand	Randomized, open-label, controlled, parallel trial	8 weeks	Rosuvastatin (10 mg QOD vs 10 mg QD)	Patients with hypercholesterolemia

5.If the results of the review have been combined, was it reasonable to do so?



- Heterogeneity was observed between studies especially in term of change in LDL-C. This heterogeneity may result from many factors including the population characteristics, and statin doses or the duration of treatment.

- A statistically significant heterogeneity was present for LDL-C (Chi2 $p < 0.0001$ and TG (Chi2 $p = 0.01$). This was resolved by sensitivity analysis that excluded the study by Rifaie et al. (Chi2 $p = 0.31$) for TG.
- However, sensitivity analysis failed to resolve the heterogeneity for LDL-C.
- For TC, no heterogeneity was present (Chi2 $p = 0.24$).

- Performed subgroup analysis
- Random-effects model was used.

Total (95% CI)	**505**	**518**	**100.0%**	**6.56 [-1.76, 14.88]**

Heterogeneity: $Tau^2 = 96.05$; $Chi^2 = 25.21$, $df = 12$ ($P = 0.01$); $I^2 = 52\%$
Test for overall effect: $Z = 1.55$ ($P = 0.12$)
Test for subgroup differences: $Chi^2 = 0.60$, $df = 3$ ($P = 0.90$), $I^2 = 0\%$

6. What are the overall results of the review?

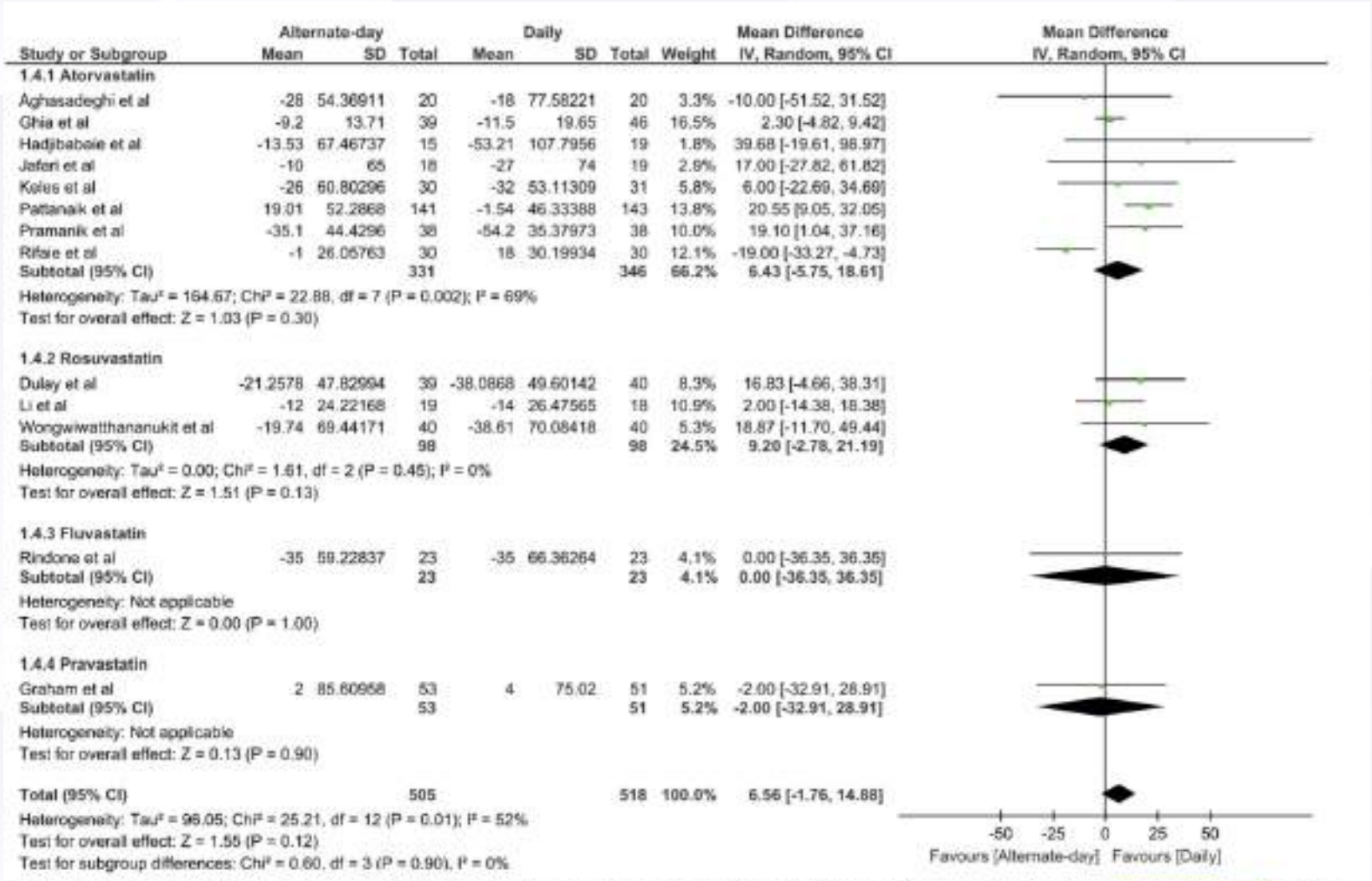
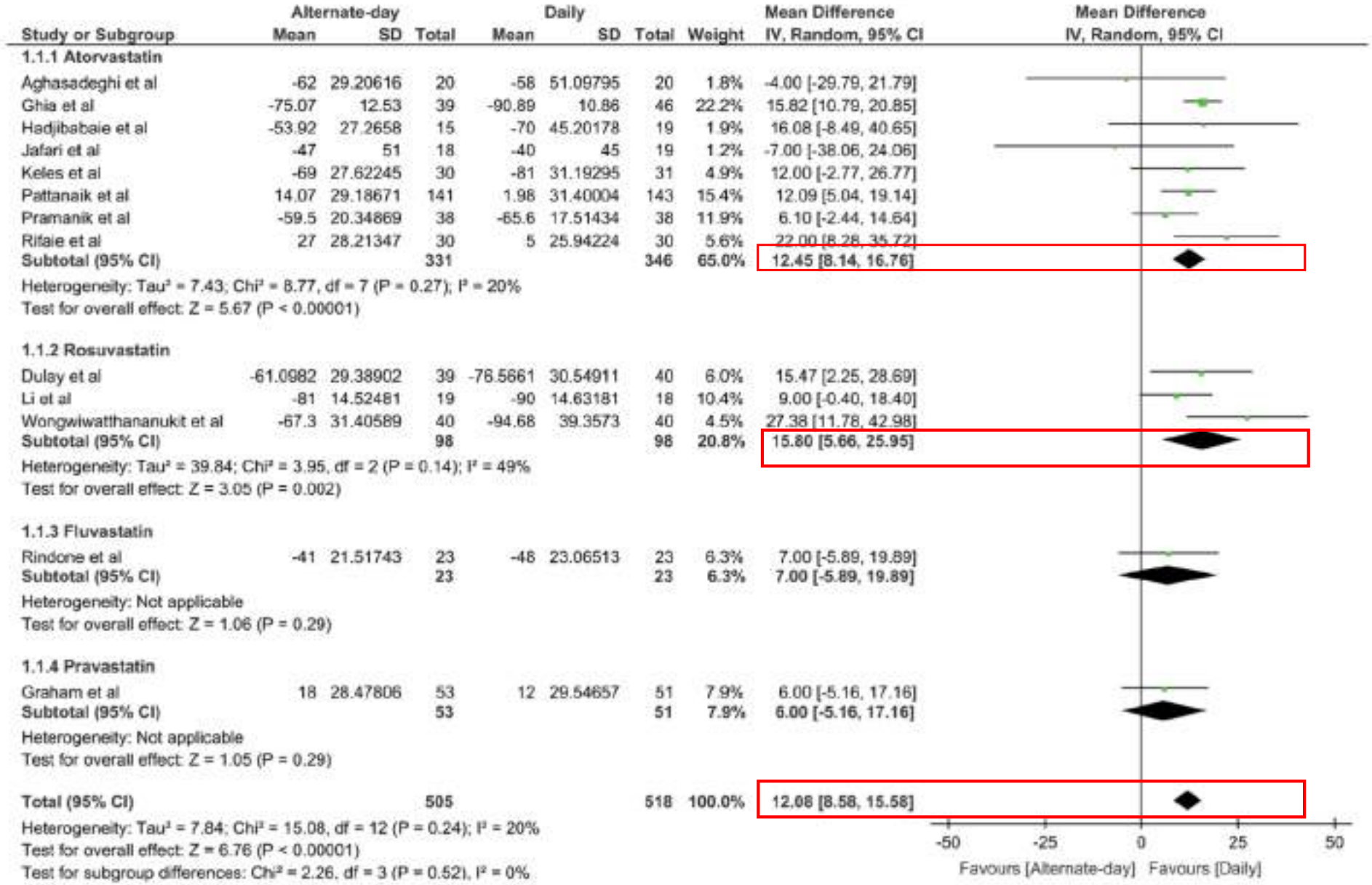


Fig. 3 Forest plot displaying the results of the meta-analysis of alternate-day dosing versus daily dosing of statin therapy on triglycerides (TGs) with subgrouping according to individual statins. *CI* confidence interval, *df* degrees of freedom, *SD* standard deviation

04 CASP Appraisal

6. What are t



Study or Subgroup	Alternate-day Mean	SD	Total	Daily Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.1.1 Atorvastatin								
Aghasadeghi et al	-62	29.20616	20	-58	51.09795	20	1.8%	-4.00 [-29.79, 21.79]
Ghia et al	-75.07	12.53	39	-90.89	10.86	46	22.2%	15.82 [10.79, 20.85]
Hadjibabaie et al	-53.92	27.2658	15	-70	45.20178	19	1.9%	16.08 [-8.49, 40.65]
Jafari et al	-47	51	18	-40	45	19	1.2%	-7.00 [-38.06, 24.06]
Keles et al	-69	27.62245	30	-81	31.19295	31	4.9%	12.00 [-2.77, 26.77]
Pattanaik et al	14.07	29.18671	141	1.98	31.40004	143	15.4%	12.09 [5.04, 19.14]
Pramanik et al	-59.5	20.34869	38	-65.6	17.51434	38	11.9%	6.10 [-2.44, 14.64]
Rifaie et al	27	28.21347	30	5	25.94224	30	5.6%	22.00 [8.28, 35.72]
Subtotal (95% CI)			**331**			**346**	**65.0%**	**12.45 [8.14, 16.76]**
Heterogeneity: Tau² = 7.43; Chi² = 8.77, df = 7 (P = 0.27); I² = 20%								
Test for overall effect: Z = 5.67 (P < 0.00001)								
1.1.2 Rosuvastatin								
Dulay et al	-61.0982	29.38902	39	-76.5661	30.54911	40	6.0%	15.47 [2.25, 28.69]
Li et al	-81	14.52481	19	-90	14.63181	18	10.4%	9.00 [-0.40, 18.40]
Wongwiwatthananukit et al	-67.3	31.40589	40	-94.68	39.3573	40	4.5%	27.38 [11.78, 42.98]
Subtotal (95% CI)			**98**			**98**	**20.8%**	**15.80 [5.66, 25.95]**
Heterogeneity: Tau² = 39.84; Chi² = 3.95, df = 2 (P = 0.14); I² = 49%								
Test for overall effect: Z = 3.05 (P = 0.002)								
1.1.3 Fluvastatin								
Rindone et al	-41	21.51743	23	-48	23.06513	23	6.3%	7.00 [-5.89, 19.89]
Subtotal (95% CI)			**23**			**23**	**6.3%**	**7.00 [-5.89, 19.89]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.06 (P = 0.29)								
1.1.4 Pravastatin								
Graham et al	18	28.47806	53	12	29.54657	51	7.9%	6.00 [-5.16, 17.16]
Subtotal (95% CI)			**53**			**51**	**7.9%**	**6.00 [-5.16, 17.16]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.05 (P = 0.29)								
Total (95% CI)			**505**			**518**	**100.0%**	**12.08 [8.58, 15.58]**
Heterogeneity: Tau² = 7.84; Chi² = 15.08, df = 12 (P = 0.24); I² = 20%								
Test for overall effect: Z = 6.76 (P < 0.00001)								
Test for subgroup differences: Chi² = 2.26, df = 3 (P = 0.52), I² = 0%								

Fig. 4 Forest plot displaying the results of the meta-analysis of alternate-day dosing versus daily dosing of statin therapy on total cholesterol (TC) with subgrouping according to individual statins. *CI* confidence interval, *df* degrees of freedom, *SD* standard deviation

6. What

Study or Subgroup	Alternate-day Mean	SD	Total	Daily Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.2.1 Atorvastatin								
Aghasadeghi et al	-84	29.61419	20	-56	46.16276	20	3.5%	-28.00 [-52.04, -3.96]
Ghia et al	-73.6	14.71	39	-93.79	17.48	46	10.2%	20.19 [13.35, 27.03]
Hadjibabaie et al	-42.27	20.83665	15	-56.05	29.37898	19	5.5%	13.78 [-3.12, 30.68]
Jafari et al	-44	47	18	-30	40	19	2.8%	-14.00 [-42.19, 14.19]
Keles et al	-71	28.47806	30	-68	25.86503	31	6.8%	-3.00 [-16.67, 10.67]
Pattanaik et al	8.18	20.07309	141	1.34	23.7743	143	11.0%	6.84 [1.73, 11.95]
Pramanik et al	-57.95	14.6502	38	-61.66	15.18272	38	10.3%	3.71 [-3.00, 10.42]
Rifaie et al	26	23.30236	30	1	19	30	8.2%	25.00 [14.24, 35.76]
Subtotal (95% CI)			331			346	**58.3%**	**6.79 [-1.59, 15.17]**
Heterogeneity: Tau² = 99.78; Chi² = 36.72, df = 7 (P < 0.00001); I² = 81%								
Test for overall effect: Z = 1.59 (P = 0.11)								
1.2.2 Rosuvastatin								
Dulay et al	-60.3248	24.74865	39	-71.1524	27.06883	40	7.9%	10.83 [-0.60, 22.26]
Li et al	-57	9.159148	19	-60	9.638983	18	10.6%	3.00 [-3.07, 9.07]
Wongwiwatthananukit et al	-65.26	27.31066	40	-87.63	37.70814	40	6.5%	22.37 [7.94, 36.80]
Subtotal (95% CI)			98			98	**24.9%**	**10.51 [-0.23, 21.26]**
Heterogeneity: Tau² = 61.27; Chi² = 6.46, df = 2 (P = 0.04); I² = 69%								
Test for overall effect: Z = 1.92 (P = 0.06)								
1.2.3 Fluvastatin								
Rindone et al	-38	22.6495	23	-44	21.93171	23	7.2%	6.00 [-6.88, 18.88]
Subtotal (95% CI)			23			23	**7.2%**	**6.00 [-6.88, 18.88]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.91 (P = 0.36)								
1.2.4 Pravastatin								
Graham et al	17	19.67232	53	12	22.27106	51	9.6%	5.00 [-3.09, 13.09]
Subtotal (95% CI)			53			51	**9.6%**	**5.00 [-3.09, 13.09]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.21 (P = 0.23)								
Total (95% CI)			505			518	**100.0%**	**7.95 [2.62, 13.29]**
Heterogeneity: Tau² = 60.33; Chi² = 44.69, df = 12 (P < 0.0001); I² = 73%								
Test for overall effect: Z = 2.92 (P = 0.003)								
Test for subgroup differences: Chi² = 0.66, df = 3 (P = 0.88), I² = 0%								

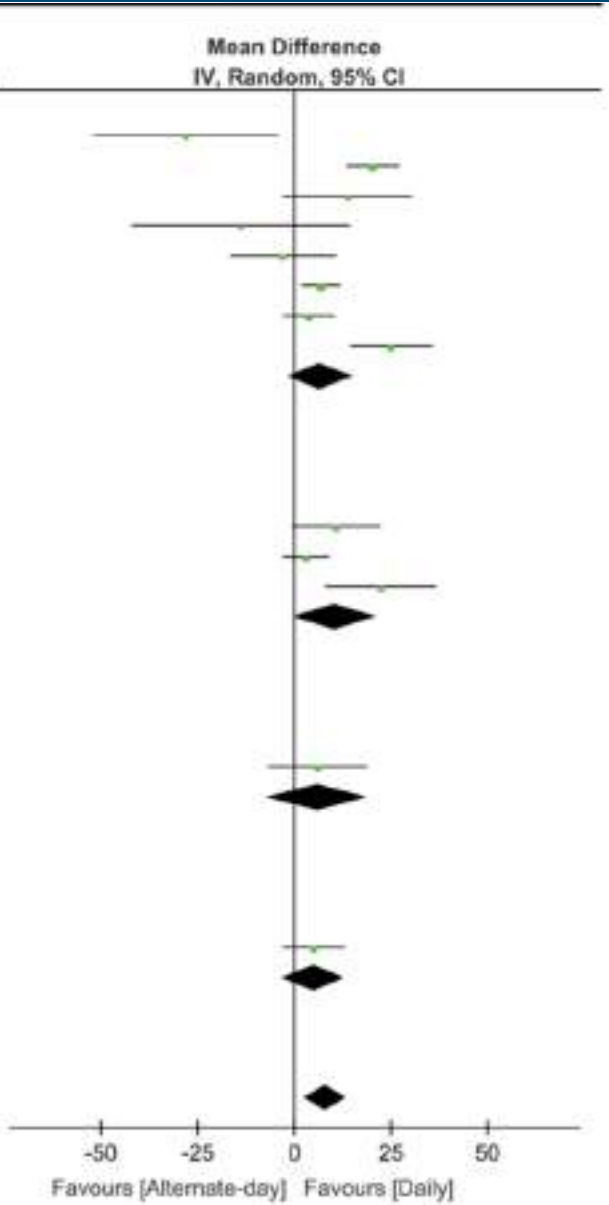
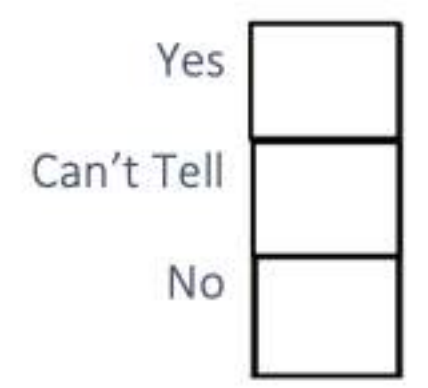


Fig. 5 Forest plot displaying the results of the meta-analysis of alternate-day dosing versus daily dosing of statin therapy on low-density lipoprotein cholesterol (LDL-C) with subgrouping according to individual statins. *CI* confidence interval, *df* degrees of freedom, *SD* standard deviation

7. How precise are the results?

- 95% confident interval was provided.
- Small sample size



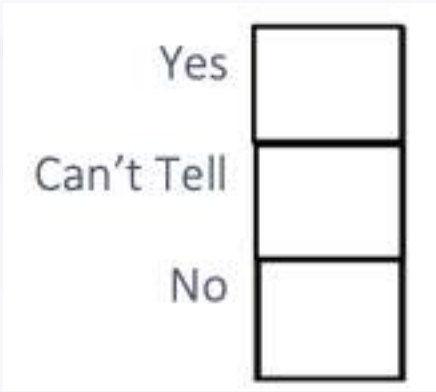
8. Can the results be applied to the local population?

				Statin used (doses)	Population
Aghasadeghi et al.	2008	Iran		Atorvastatin (20 mg QOD vs 20 mg QD)	Patients with hypercholesterolemia
Dulay et al.	2009	Canada		Rosuvastatin (20 mg QOD vs 10 mg QD)	Patients with hypercholesterolemia
Ghia et al.	2014	India			
Graham et al.	2002	USA		Atorvastatin (10 mg QOD vs 10 mg QD)	Naïve patients of dyslipidemia
Hadjibabaie et al.	2007	Iran		Pravastatin (same dose QOD vs half dose as before QD)	Patients who were receiving pravastatin daily and had maintained their NCEP-defined LDL-C goal for at least 3 months
Jafari et al.	2003	USA		Atorvastatin (10 mg QOD vs 10 mg QD)	Patients with type 2 DM with hypercholesterolemia
Keles et al.	2008	Turkey		Atorvastatin (10 mg QOD vs 10 mg QD)	Patients with LDL-C of 100 to 200 mg/dL
Li et al.	2012	China	37人	Atorvastatin (20 mg QOD vs 20 mg QD)	Patients with serum TC levels >200 mg/dL and LDL-C levels >130 mg/dL
Pattanaik et al.	2012	India		Rosuvastatin (10 mg QOD vs 10 mg QD)	Patients with LDL-C ≥160 mg/dL and/or TG ≥200 mg/dL
				Atorvastatin (same dose as before QOD vs same dose as before QD)	Patients who were receiving atorvastatin for at least 6 months and had met their NCEP-defined LDL-C goal
Pramanik et al.	2012	India		Atorvastatin (20 mg QOD vs 20 mg QD)	Patients with hypercholesterolemia
Rifaie et al.	2012	Egypt		Atorvastatin (10 mg QOD vs 10 mg QD)	Patients with CAD
Rindone et al.	1998	USA		Fluvastatin (40 mg QOD vs 20 mg QD)	Patients with a LDL-C level >160 mg/dL despite at least 3 months of a low-fat diet
Wongwiwatthananukit et al.	2006	Thailand	80人	Rosuvastatin (10 mg QOD vs 10 mg QD)	Patients with hypercholesterolemia

Yes	
Can't Tell	
No	

佔比:117/1023=11.4%

8. Can the results be applied to the local population?

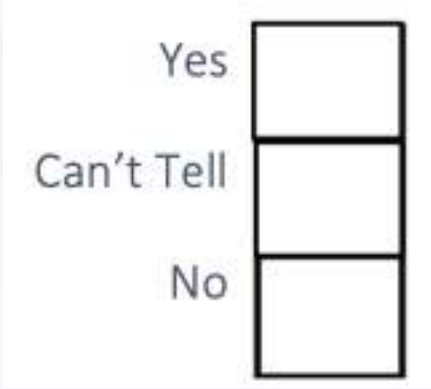


84歲姜先生，罹患有第二型糖尿病、糖尿病腎病變、高血壓、混合型高血脂

藥品名稱	劑量	頻次	途徑
Semaglutide injection-4mg/vial	1 mg	QW	Subcutaneous
Glimepiride-2mg	0.5 tablet	QDAC	Oral
Pioglitazone-30 mg	1 tablet	QD	Oral
Rosuvastatin-10mg	1 tablets	QOD	Oral
Pentoxifylline-400 mg	1 tablet	BID	Oral

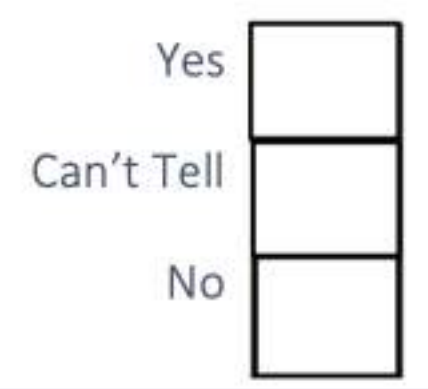
9.Were all important outcomes considered?

Study	Adverse events (AEs)
Aghasadeghi et al.	No AEs
Dulay et al.	One patient experienced myalgia without a rise in CK, which resolved with time. Gastrointestinal upset was the most common complaint
Ghia et al.	- *Daily dosing group*: 1 headache, 1 asthenia, 2 dizziness, 3 parasthesia, 1 depression, 1 myalgia and 1 elevated liver enzymes - *Alternate-day dosing group*: 1 headache, 1 dyspepsia, 1 dizziness and 1 parasthesia
Graham et al.	One complained of heartburn and myalgia at the 4-month visit
Hadjibabaie et al.	No AEs
Jafari et al.	No AEs
Keles et al.	No AEs
Li et al.	Not reported
Pattanaik et al.	One patient experienced myalgia without a rise in CK
Pramanik et al.	One patient experienced myalgia in daily dosing group
Rifaie et al.	No AEs
Rindone et al.	Two patients experienced gastrointestinal upset and one patients experienced urinary retention
Wongwiwatthananukit et al.	Two patients in the daily dosing group experienced malaise and myalgia and one patient in the alternate-day dosing group developed headache



- Most of the included studies did not report the incidence of AEs in each group separately.
- Could not pool the AEs in a meta-analysis model.
- The included studies did not use a standardized tool to assess statin-associated adverse muscle symptoms.
- The issue of compliance with the alternate-day dosing has been a limitation to this regimen

10. Are the benefits worth the harms and costs?



- Further large- scale RCTs with long-term treatment are recommended to confirm these findings and investigate the effects of alternate-day dosing of statins vs daily dosing on patient compliance particularly in patients with statin-associated adverse muscle symptoms (SAMS), risk of new onset DM and CV events.
- More RCTs are needed to investigate the efficacy of other statin regimens (e.g., twice or once weekly) compared with daily and alternate-day regimens.

- Lower cost
- Uncertain compliance
- No significant difference in efficacy
- Well-tolerated

第 5 部分

Conclusion

My opinion

- In conclusion, this meta-analysis shows that alternate-day dosing of individual statins (especially atorvastatin and rosuvastatin) is as efficacious as daily dosing on LDL-C and TG.
- Further large- scale RCTs are recommended to confirm and extend these findings.

- It is not possible to directly determine whether alternate-day regimen reduces muscle-related side effects.
- It might be a reasonable choice for our patient since there were no obvious harm.

My opinion

醫師調整rosuvastatin的給藥方法，是否能維持相同的降血脂效果？

-隔日給藥對於LDL-C及TG的效果和每日給藥無顯著差異。但對改善TC而言可能還是每日給藥的效果較為顯著。

是否能減少藥物的不良反應？

-目前的證據無直接顯示不同給藥方式對於肌肉疼痛等不良反應是否有差異，目前臨床上若有產生不良反應換一種statin、降低劑量或給藥頻率都是可嘗試的方式，針對這位病人我認為還是可以嘗試採用隔日給藥的方式，若仍無法耐受可考慮改用其他statin或其他降血脂藥物。

諮詢藥師應如何衛教姜先生？

-醫師開立rosuvastatin每兩天使用一次，應規律服用藥物，盡量不要忘記服用，忘記吃藥想起時應儘快服用，若已接近下次服藥時間則不必補服。

不良反應仍須觀察有無持續出現。應配合定期回診並抽血追蹤血脂狀況。

THANKS