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# Meta-analysis of the comparative efficacy and safety of pitavastatin and atorvastatin in patients with dyslipidaemia

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## SUMMARY

***What is known and Objective:*** **Pitavastatin is the latest available statin. It has been shown to be effective in the treatment of dyslipidaemia. This meta-analysis was aimed at evaluating the effects of pitavastatin on lipid profiles in patients with dyslipidaemia compared with atorvastatin.**

***Methods:*** **Clinical trials were identified through electronic searches (MEDLINE, CINAHL, EBM review, and the Cochrane Library) up to January 2011 and historical searches of relevant articles. Studies were included in the meta-analysis if they were (i) randomized controlled trials that evaluated pitavastatin at the recommended dose vs. atorvastatin in patients with dyslipidaemia, (ii) lasting at least 6 weeks, (iii) reporting total cholesterol (TC), LDL-C, HDL-C or triglyceride (TG) levels and (iv) published in English. Treatment effect was estimated with the mean difference in the per cent changes in lipid profiles from baseline to final assessment between pitavastatin and atorvastatin.**

***Results:*** **Seven trials involving 1529 patients were included. Pitavastatin reduced LDL-C level as effectively as atorvastatin (mean difference 0.97%, 95% CI −0.48% to 2.42%). The reductions in TC and TG levels were also comparable between the two drugs. The mean differences were 1.22% (95% CI −0.55% to 2.99%) and 2.3% (95% CI −1.06% to 5.65%), respectively. However, HDL-C levels increased significantly more with pitavastatin than with atorvastatin (mean difference 1.78%, 95% CI 0.20–3.36%, $P = 0.03$).**

***What is new and Conclusions:*** **Pitavastatin was as effective as atorvastatin in lowering LDL-C, TC and TG levels. Pitavastatin was marginally superior to atorvastatin in increasing HDL-C levels.**

## WHAT IS KNOWN AND OBJECTIVE

Statins are effective and remain the first-choice treatment for dyslipidaemia. It reduces the risk of coronary heart disease (CHD) in both primary and secondary prevention.[1,2] Atorvastatin is a potent and the most widely used statin. Its effectiveness in lowering LDL cholesterol and total cholesterol (TC) has been demonstrated in a number of trials.[3–5] However, it is metabolized by CYP3A4 and is therefore at an increased risk of drug–drug interactions. Pitavastatin is the latest addition to the statin group. Approved for use in Japan, Korea, Thailand, China, the USA and the UK,[6,7] it is indicated for primary hyperlipidaemia and mixed dyslipidaemia as an adjunctive therapy to diet for reducing TC, low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (Apo B), triglycerides (TGs), and to increase high-density lipoprotein cholesterol (HDL-C).[8] After oral administration, the peak plasma concentration is achieved in approximately 1 h, and the absolute bioavailability is about 50%. Similar to other statins, pitavastatin is extensively bound to plasma protein (99%).[8] Unlike simvastatin, lovastatin, fluvastatin and atorvastatin, pitavastatin is minimally metabolized by cytochrome P450 and is converted to pitavastatin lactone, an inactive form, via glucuronidation by uridine diphosphate-glucuronosyltransferase.[6] Its low potential to interact with other drugs may offer an advantage over other statins. Several clinical trials have evaluated the efficacy of pitavastatin against simvastatin,[9,10] pravastatin[11] and atorvastatin[7,12–14] in patients with dyslipidaemia. To the best of our knowledge, there has been no previously published systematic review and meta-analysis of pitavastatin. We therefore undertook a systematic review and meta-analysis in an attempt to determine the comparative efficacy and safety of pitavastatin vs. atorvastatin in the treatment of dyslipidaemia.

## METHODS

### *Identification of studies*

Reports of randomized controlled trials of pitavastatin were identified through a systematic search on MEDLINE, CINAHL, EBM review and the Cochrane Library. The bibliographic databases were searched from their respective inceptions to January 2011. The MeSH search terms used were 'pitavastatin', 'atorvastatin', 'dyslipidaemias', 'hyperlipidaemias' and 'randomized controlled trial'. This was followed by a keyword search using 'nisvastatin', 'itavastatin', 'dyslipoproteinaemia' and 'hyperlipaemias' as keywords. The reference lists of relevant articles were also scanned to identify possible published trials.

### *Study selection*

Studies were included in the meta-analysis if they were (i) randomized controlled trials that evaluated pitavastatin at the recommended dose (2–4 mg) vs. atorvastatin in patients with

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**Table 1.** Characteristics of randomized controlled trials included in the meta-analysis

| Study | Quality score | Location | Inclusion criteria | Intervention | *N* | Treatment duration | Data analysis | Any adverse events |
|---|---|---|---|---|---|---|---|---|
| Budinski *et al.*[7] | 4 | Denmark, India, Russia, Spain | Men and non-pregnant, non-lactating women<br>Aged 18–75 years<br>Diagnosed with primary hypercholesterolaemia or combined dyslipidaemia<br>Fasting LDL-C levels 160–220 mg/dL and TG levels ≤ 400 mg/dL | I: pitavastatin 2 mg or atorvastatin 10 mg once daily<br>II: pitavastatin 4 mg once daily (force-titrated from 2 mg/day) or atorvastatin 20 mg once daily (force-titrated from 10 mg/day) | P: 316<br>A: 102<br><br><br><br>P: 300<br>A: 103 | 12 weeks | ITT | P 18% (110/616)<br>A 20% (40/205) |
| Lee *et al.*[12] | 3 | Korea | Men and women aged 20–79 years with untreated hypercholesterolaemia<br>LDL-C > 130 mg/dL<br>TG levels < 400 mg/dL | Pitavastatin 2 mg or atorvastatin 10 mg once daily | P: 110<br>A: 112 | 8 weeks | PP | P 19.1% (26/136)<br>A 25% (33/132) |
| Yokote *et al.*[13] | 3 | Japan | Men and women aged ≥ 20 years with hypercholesterolaemia (TC ≥ 220 mg/dL) including familial hypercholesterolaemia<br>TG levels < 400 mg/dL | Pitavastatin 2 mg or atorvastatin 10 mg once daily | P: 101<br>A: 103 | 12 weeks | PP | P 10.9% (11/101)<br>A 8.7% (9/103) |
| Sasaki *et al.*[14] | 3 | Japan | Men or post-menopausal women aged ≥ 20 years<br>LDL-C level ≥ 140 mg/dL<br>HDL-C levels < 80 mg/dL<br>TG levels < 500 mg/dL<br>Had glucose intolerance | Pitavastatin 2 mg or atorvastatin 10 mg once daily | P: 103<br>A: 104 | 52 weeks | PP | P 9% (9/96)<br>A 14% (13/93) |
| Sakabe *et al.*[25] | 2 | Japan | Primary hypercholesterolaemia<br>LDL-C levels > 160 mg/dL and TG levels < 400 mg/dL while on diet therapy | Pitavastatin 2 mg or atorvastatin 10 mg once daily | P: 37<br>A: 34 | 3 months | ITT | NR |
| Nozue *et al.*[26] | 2 | Japan | Heterozygous familial hypercholesterolaemia | Pitavastatin 2 mg or atorvastatin 10 mg once daily | P: 8<br>A: 9 | 12 weeks | ITT | NR |
| Kawashiri *et al.*[27] | 3 | Japan | Heterozygous familial hypercholesterolaemia | Pitavastatin 4 mg or atorvastatin 20 mg once daily | P: 19<br>A: 19 | 8 weeks | ITT | NR |

A, atorvastatin; ITT, intention to treat; NR, not reported; P, pitavastatin; PP, per protocol.

dyslipidaemia, (ii) lasting at least 6 weeks, (iii) reporting TC, LDL-C, HDL-C or TG levels and (iv) published in English.

### *Data extraction and quality assessment*

Data extraction and study quality assessment were performed independently by two investigators using a standardized form. Disagreements were resolved by a third investigator. The data abstracted were the year of publication, study location, study design, patient characteristics, number of patients, treatment regimen, outcome measures and adverse effects. The methodological quality of study was assessed using the scale developed by Jadad *et al.*[15] The scale focuses exclusively on the three dimensions of internal validity, i.e. randomization, blinding and patient attrition. A study with a score of 3 or more out of 5 points was considered high quality.

### *Statistical analysis*

The primary outcome was the per cent change from baseline in LDL-C level. Secondary outcomes included the per cent changes from baseline in TC, HDL-C and TG levels. When the variances of these changes were not provided, they were estimated using the pooled estimate from the studies that reported the variances. Treatment effect was estimated with mean difference in the per cent changes from baseline in lipid profiles between pitavastatin and atorvastatin. Adverse effects were expressed as risk ratio (RR). The inverse variance-weighted method was used for the pooling of mean difference and the estimation of 95% confidence interval.[16] A random effects model was used when the Q-statistic for heterogeneity was significant at the level of 0.1;[17] otherwise, the fixed effects model was used.[16] The degree of heterogeneity was quantified using I-squared statistic, which is an estimate of the percentage of total variation across studies owing to heterogeneity.[18] A funnel plot and the method of Egger *et al.*[19] were performed to assess publication bias. The statistical analysis was undertaken with RevMan® version 5.0.25. (Cochrane Collaboration, Oxford, UK) *P*-value of <0.05 was considered to be statistically significant.

## RESULTS

### *Study characteristics*

Twelve randomized controlled trials of pitavastatin vs. atorvastatin were identified. Three studies enrolled patients with acute coronary syndrome and were then excluded.[20–22] One trial was further excluded as it evaluated low-dose pitavastatin (1 mg).[23] The remaining eight studies met our inclusion criteria. However, one was a subanalysis report[24] of the major study already included.[13] This subanalysis report was therefore excluded. Seven trials were eventually included in our meta-analysis.[7,12–14,25–27] Six trials compared pitavastatin 2 mg against atorvastatin 10 mg,[7,12–14,25,26] and two trials compared pitavastatin 4 mg against atorvastatin 20 mg.[7,27] Of note, one study compared pitavastatin 2 and 4 mg against atorvastatin 10 and 20 mg, respectively.[7] The characteristics of the 7 included trials are summarized in Table 1.

### *Effects on lipid profiles*

One thousand five hundred and twenty-nine patients were included in the seven trials that reported the per cent changes from baseline in LDL-C level.[7,12–14,25–27] Pitavastatin was as effective as atorvastatin in reducing LDL-C level (mean difference 0.97%, 95% CI −0.48% to 2.42%) (Fig. 1). No evidence of publication bias was detected. (Egger bias −0.51; 95% CI −4.12 to 3.11, $P = 0.7439$) (Fig. 2). No significant differences were found between pitavastatin and atorvastatin in their effects on TC and TG levels (Figs 3 and 4). The pooled mean differences were 1.22% (95% CI −0.55% to 2.99%) and 2.3% (95% CI −1.06% to 5.65%), respectively. Pitavastatin was superior to atorvastatin in elevating HDL-C levels (mean difference 1.78%, 95% CI 0.20–3.36%, $P = 0.03$) (Fig. 5).

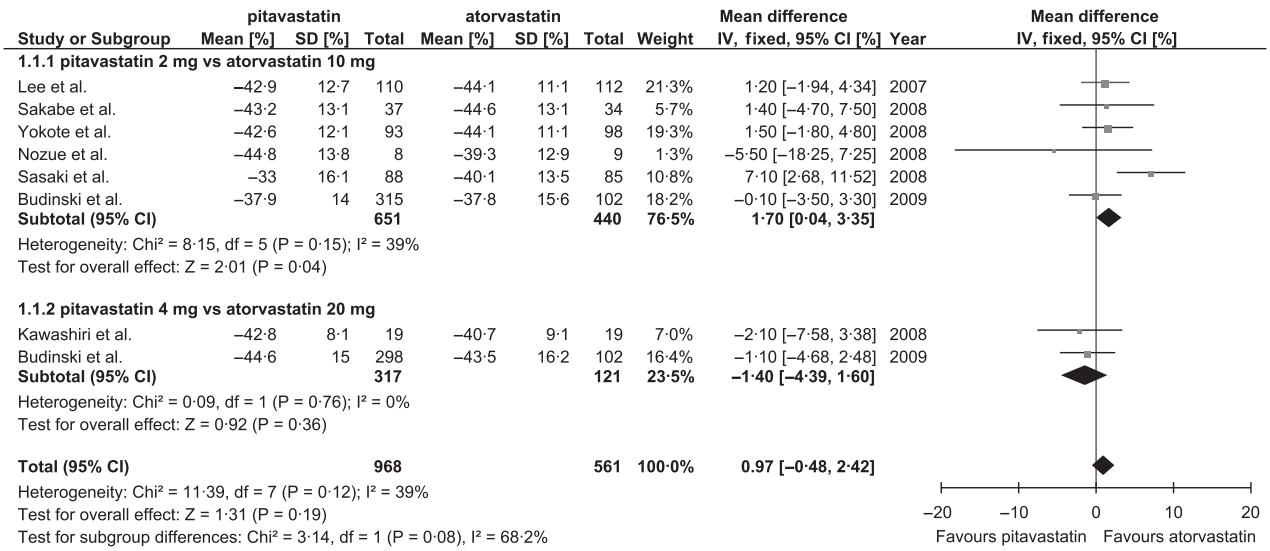


**Fig. 1.** Mean differences (95% CI) in the per cent changes in LDL-C level.

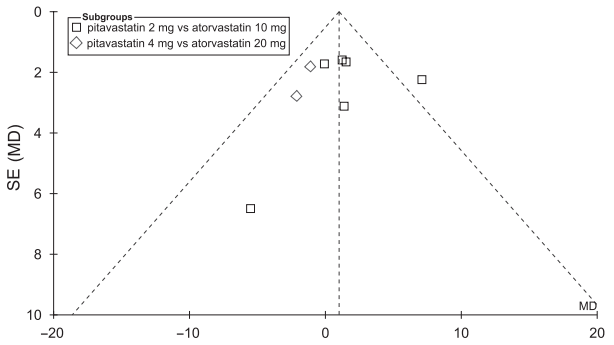


**Fig. 2.** Funnel plot of the studies included.

### *Safety*

Four trials[7,12–14] reported the number of patients who experienced at least one treatment-related adverse event that could be transformed to adverse events rate. The risk of any adverse events did not differ between pitavastatin and atorvastatin (RR 0.87, 95% CI 0.68–1.10). The adverse events commonly reported among the two groups were gastrointestinal symptoms, myalgia, fatigue and headache.

## DISCUSSION

Accumulating evidence has linked elevated TC, LDL-C and TG levels and reduced HDL-C levels to the development of CHD. A large number of clinical trials and meta-analyses have shown

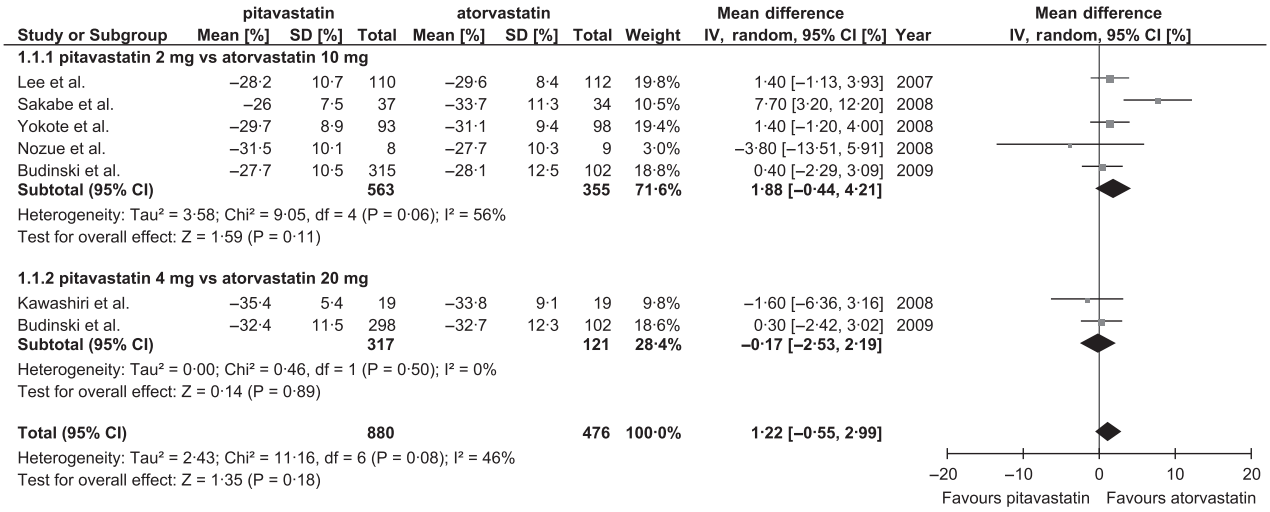


**Fig. 3.** Mean differences (95% CI) in the per cent changes in total cholesterol level.

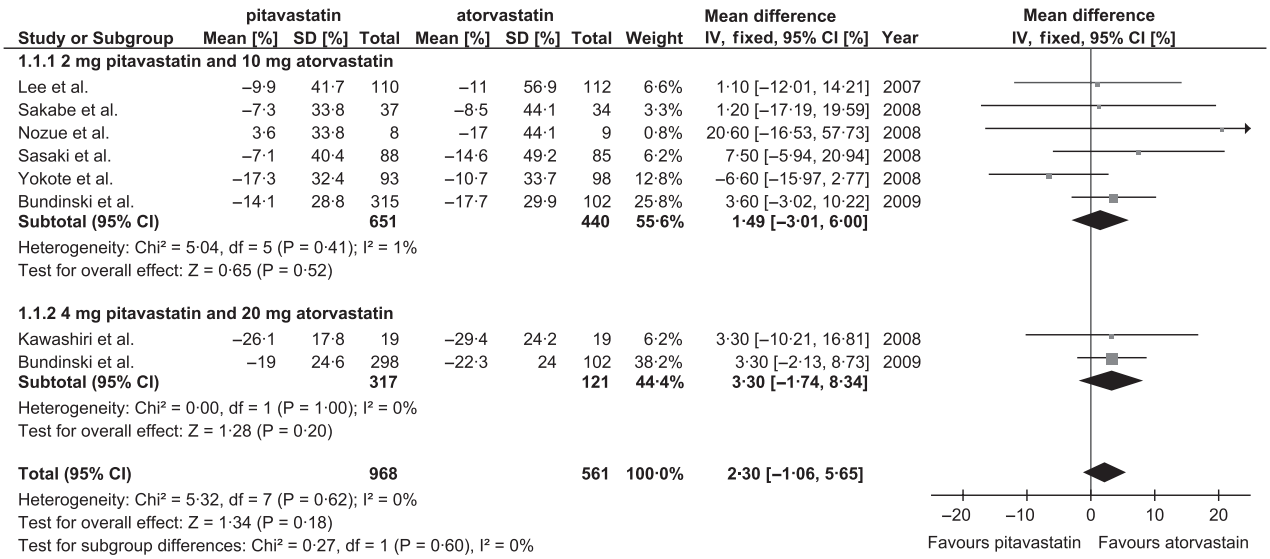


**Fig. 4.** Mean differences (95% CI) in the per cent changes in triglyceride level.

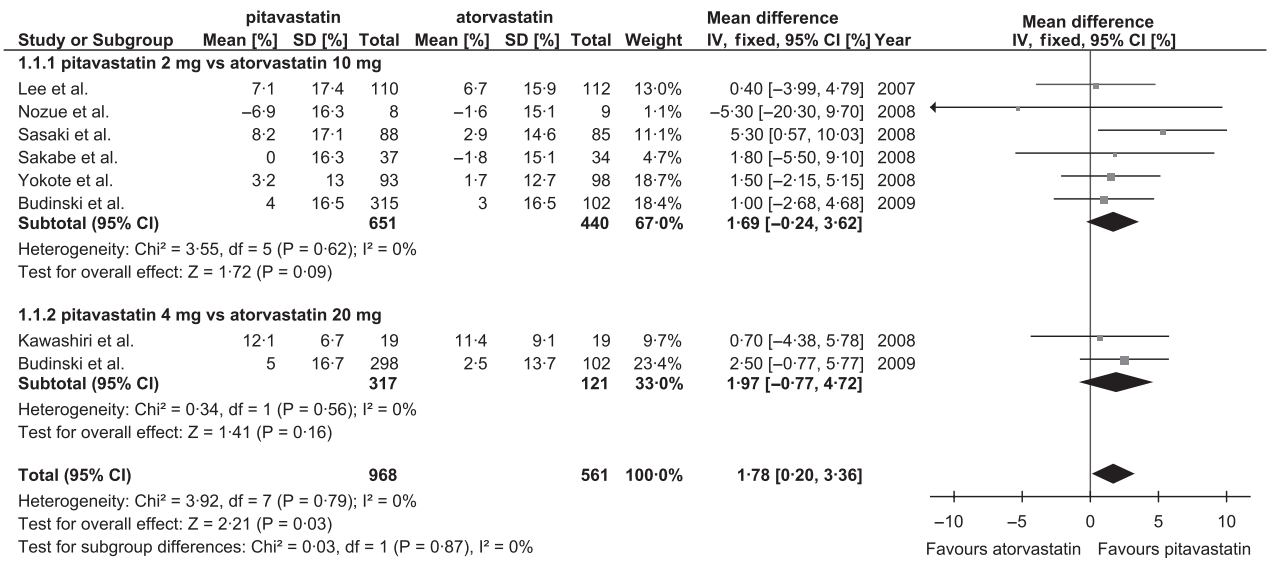


**Fig. 5.** Mean differences (95% CI) in the per cent changes in HDL-C level.

that a decrease in LDL-C reduced the risk of CHD.[1,2,28–31] Elevated LDL-C is therefore identified as the primary target of lipid-lowering therapy as recommended by the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III).[32] The primary goal of therapy is also the lowering of LDL-C level. These goals can be achieved mainly by therapeutic lifestyle changes (TLC) and pharmacotherapy. The level of initiation of TLC and drug therapy varies depending on CHD risk of individual patients. LDL-lowering drugs include statins, bile acid sequestrants, niacin, fibrates and cholesterol absorption inhibitors. Among these, statins remain the drug of choice as they possess the most potent LDL-lowering effect. [32,33]. The currently available statins include simvastatin, lovastatin, fluvastatin, pravastatin, atorvastatin, rosuvastatin and pitavastatin.

Pitavastatin is the latest addition to the statin group. It was developed in Japan and has been available there since 2003 for the treatment of hypercholesterolaemia.[34] It was approved for use in the United States in 2009.[6] As with other statins, pitavastatin reduces cholesterol synthesis in the liver by competitively and strongly inhibits 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase. It also induces the expression of LDL receptors, resulting in increased hepatic uptake of LDL-C from the circulation, hence its LDL-C-lowering ability. In addition, pitavastatin inhibits the secretion of VLDL from the liver, leading to a reduction in plasma TG levels. HDL-elevating effect of pitavastatin is attributable to an increase in the secretion of ApoA-I, a constituent of HDL, from the liver.[35] The recommended starting dose is 2 mg once daily, with a maximum of 4 mg daily. Pitavastatin can be taken irrespective of timing of food intake or time of the day.[8]

Although a number of head-to-head trials of pitavastatin have been published, the majority of them compared the drug with atorvastatin, the most widely used statin. Data from seven trials were pooled with a total of 968 patients in the pitavastatin group and 561 patients in the atorvastatin group. LDL-C level was used as the primary outcome as it is the primary target of lipid-lowering therapy according to NCEP ATP III guideline.[32] The effect of pitavastatin on LDL-C levels did not differ from that of atorvastatin. Pitavastatin was also as effective as atorvastatin in reducing TC and TG levels. Our results were contrast with the results from *in vitro* studies. In HepG2 cell, pitavastatin inhibited HMG-CoA reductase more effectively than did atorvastatin. Moreover, at doses with comparable degree of inhibition of cholesterol synthesis, pitavastatin induced LDL receptor to a greater extent than did atorvastatin.[36] Pitavastatin increased HDL-C levels better than did atorvastatin (mean difference 1.78%, 95% CI 0.20–3.36%, $P = 0.03$). The secretion of apolipoprotein A-I (apoA-I), an essential component of HDL, has been thought to be the mechanism of HDL-elevating action of statins. Pitavastatin has been reported to increase production of apoA-I in HepG2 cells more efficiently than atorvastatin.[37] In addition, it has been shown to stimulate lipoprotein lipase activity more potently than atorvastatin. This may facilitate an increase in HDL-C through the efficient metabolism of TG-rich lipoproteins.[38] These may explain the superiority of pitavastatin over atorvastatin regarding the effect on HDL as demonstrated in our meta-analysis. Both pitavastatin and atorvastatin were well tolerated. No significant difference was found in the risk of adverse events. Those commonly reported among the two groups were gastrointestinal symptoms, myalgia, fatigue and headache. The majority were mild to moderate in intensity. An elevation in ALT value >3 times the upper limit of normal was reported in two patients treated with pitavastatin and none treated with atorvastatin.[14] No patients had creatinine kinase values >10 times the upper limit of normal.[7,12–14] The results of this meta-analysis were not surprising given that pitavastatin at the recommended doses (2 and 4 mg once daily) was compared against atorvastatin at low doses (10 and 20 mg once daily). Atorvastatin has been reported to reduce LDL-C and TG levels in a dose-dependent manner.[39]

It is worth noting limitations of individual studies included in the meta-analysis. Most of them were open-label design.[12–14,25–27] The sample sizes were also small.[25–27] Only one trial was long in duration of treatment,[14] and the rest were

short-term ranging from 6 to 12 weeks.[7,12,13,25–27] Most were conducted in Asian populations, particularly in Japanese subjects. In addition, several studies analysed the efficacy results on a per protocol basis.[12–14] These may introduce a bias in the study results. Also, our meta-analysis was not without shortcomings. Only trials published in English were included. Pitavastatin was first discovered in Japan, and there might be clinical trials published in Japanese in local journals that are not indexed in international bibliographic databases. Not including any such trials may raise the possibility of missing relevant data and publication bias. Egger's method[19] was used to assess possible publication bias. There was no obvious evidence of bias with respect to the pooling of the primary outcome.

## WHAT IS NEW AND CONCLUSIONS

To the best of our knowledge, this is the first systematic review and meta-analysis of the efficacy and safety of pitavastatin in the treatment of dyslipidaemia. The available evidence suggests that pitavastatin and low-dose atorvastatin have comparable efficacy and safety in the treatment of dyslipidaemia. However, pitavastatin raises HDL-C level significantly more than atorvastatin. It also has low potential for cytochrome P450-mediated drug–drug interactions. Its effectiveness relative to higher doses of atorvastatin remains to be investigated. In addition, the comparative long-term effects of pitavastatin relative to other statins remain to be established.

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