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REVIEW ARTICLE

# Pitavastatin: Coronary Atherosclerotic Plaques Changes and Cardiovascular Prevention

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**Abstract**
Stains remain the first therapeutic approach in patients with dyslipidemia to control plasma lipids levels and cardiovascular risk. Multiple clinical trials have demonstrated the benefits of statins in reducing major cardiovascular adverse events in primary and secondary prevention. Moreover, in patients with coronary artery disease, statins decrease coronary atherosclerotic plaque volume and composition, inducing atheroma stabilization. Pitavastatin, is a new-generation lipophilic statin, indicated for the treatment of dyslipidemia and prevention of cardiovascular diseases. The purpose of this review, the first at our knowledge on this topic, is to summarize and examine the current knowledge about the effectiveness of pitavastatin in patients with coronary artery disease. The available data suggest that pitavastatin significantly, lowers the rate of adverse cardiovascular events, in patients at a high risk of atherosclerotic disease, with stable angina pectoris or with acute coronary syndrome. Moreover intravascular ultrasound have shown that pitavastatin induces favorable changes in plaque morphology, increasing the fibrous cap thickness, and decreasing both plaque and lipid volume indexes. Globally the efficacy of pitavastatin is greater or similar to other statins.

**Keywords** Pitavastatin · Cardiovascular prevention · Atherosclerotic plaque · Thin cap fibroatheroma · Dyslipidemia

## 1 Introduction

Statins are still the mainstay for treatment of dyslipidemia and cardiovascular prevention [1]. Reduction cholesterol plasma levels is associated with a significant decrease of cardiovascular outcomes [2].This beneficial effect has been obtained with all available statins [3], particularly with high doses, to reach intensive reduction of LDL-C [1, 4].

Coronary atherosclerosis is considered a chronic low-grade inflammatory disease, triggered by atherogenic lipoprotein (particularly oxLDL-C), reactive oxygen species, pro-inflammatory cytokines and macrophages infiltration into the arterial wall [5–7]. While most atherosclerotic plaques remain stable and silent for a long time, leading to slow progressive coronary narrowing, others become suddenly unstable or so called "vulnerable". Intracoronary imaging have shown that the key aspect of a vulnerable plaque is the presence of a lipid rich core, (necrotic in some lesions) with an overlying thin fibrous cap < 65 microns [7–10]. It is now well established that thin-cap fibroatheroma (TCFA), plays a major role in plaque rupture, with subsequent coronary thrombosis [7–12].

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Clinically these changes lead to acute coronary syndrome (ACS), including myocardial infarct, unstable angina, or cardiac arrest. Moreover vulnerable plaques are strongly and independently predictive of subsequent major acute cardiovascular events (MACE). This relationship has been well demonstrated in the PROMISE, PROSPECT, VIVA, and ATHEROREMO-IVUS studies [11, 13–15].

However, despite successful revascularization, there is evidence of a significant residual risk of future cardiovascular events, for different reasons: non-culprit thin cap fibroatheroma progression, incomplete revascularization, high plaque burden, persistent risk factors or increased inflammatory status [16–18].These findings emphasize the importance of an early identification and treatment of vulnerable plaques to avoid ACS.

Patients with coronary heart disease are recommended to use statins to reduce the risk of acute coronary syndrome. In addition to lower plasma lipids, there is growing evidence that statins, increasing fibrous cap thickness, have a beneficial effect in atheroma progression and in stabilizing high-risk coronary plaques [4, 19, 20].

Pitavastatin, a new-generation lipophilic statin, approved by the Food and Drugs Administration (FDA) and European Medicines Agency (EMA) is indicated for the treatment of dyslipidemia and prevention of cardiovascular diseases. Pitavastatin, 2 and 4 mg, is available in several countries, as brand or generics. The lipid lowering of the drug is either similar, or even greater [21–23] than that of other statins, with a high prevalence of patients achieving LDL-C target [21]. Globally pitavastatin, decreases total cholesterol (22–39%), LDL-C (40 to ~ 50%) and triglycerides (13–32%), according to approved dosage and increases HDL lipoproteins [21, 24, 25].

Recently, a large meta-analysis has reported, that pitavastatin (1 mg to 16 mg/day), is more potent than atorvastatin, rosuvastatin, and fluvastatin in reducing LDL-C [26]. However 16 mg/day is out of the approved and common therapeutic dosage. Considering the relationship between LDL-C and risk of major cardiovascular events ESC/EAS and ACC/AHA guidelines [1, 27] recommend statins not only for secondary, but also for primary cardiovascular prevention, according to LDL-C level and total cardiovascular risk.

The aim of this review, the first at our knowledge on this topic, is to summarize the relevant literature on the role of pitavastatin on primary and secondary cardiovascular prevention and, particularly, on quantitative and qualitative aspect of coronary atherosclerotic plaques.

A literature search was conducted in PubMed and EMBASE, using the keywords pitavastatin, coronary artery disease, cardiovascular prevention, atherosclerotic coronary plaques, to identify relevant scientific articles. We did not consider short communications, editorials and posters. Moreover we did not report changes in lipids, because beyond the scope of this review. The resulting articles were evaluated by the authors for suitability for the review.

A total of 42 publications were identified and evaluated, 29 were excluded and 13 were eligible and included in the review (Fig. 1). Overall a total of 8515 patients (age 61.4–68.1 years), were treated with pitavastatin during 2 to 240 weeks (Table 1). Pitavastatin (2–4 mg/day) was compared with low dose (1 mg/day), with placebo/diet, atorvastatin, (10–20 mg/day), pravastatin (10 mg/day), fluvastatin

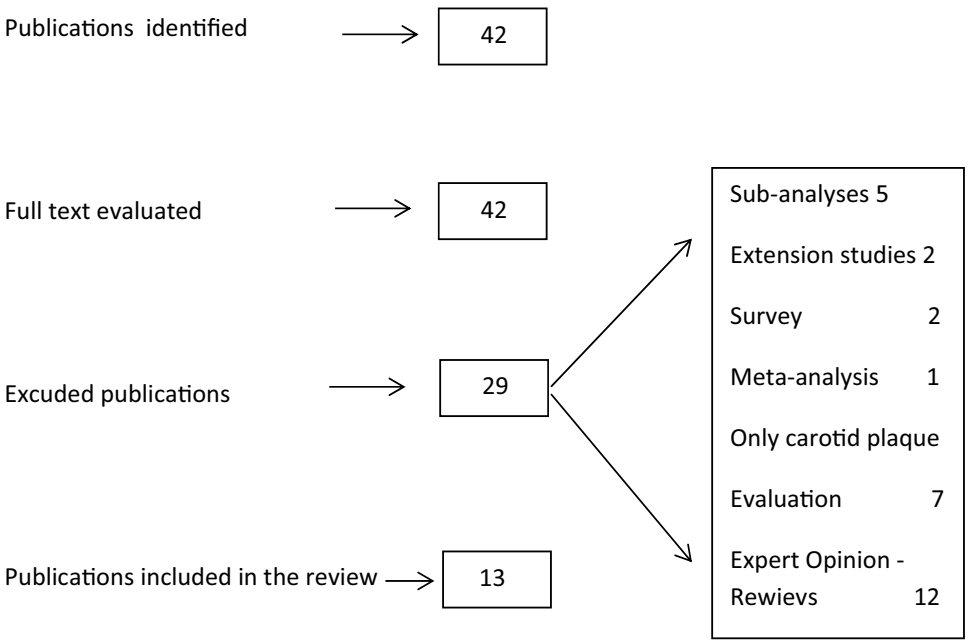



**Fig. 1** Flowchart

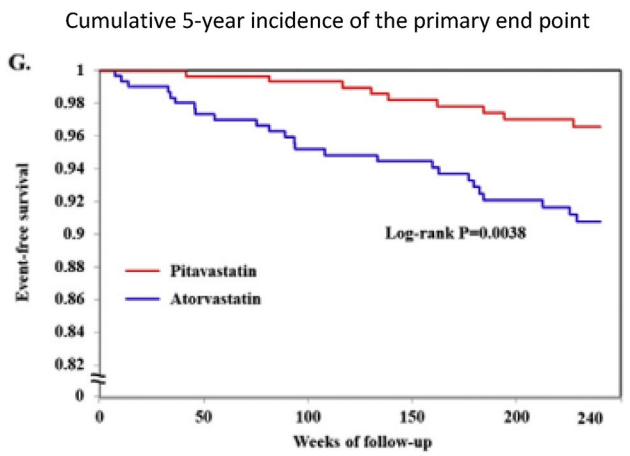
**Table 1** Demographic characteristics of included studies

| Study | Design | Diagnosis | Drug, dose, duration | N° pts | Age (years) | Control, dose, duration | N° pts | Age (years) |
|---|---|---|---|---|---|---|---|---|
| TOHO-LIP [23] | Open, randomized, blind end points | Dyslipidemia, High CV risk factors | P 2 mg 240 weeks | 312 | 65.3 | At 10 mg 240 weeks | 310 | 65.4 |
| Real-CAD [28] | Prospective; randomized; blinded end points | Stable CAD | P 4 mg 3.9 years | 6199 | 68.1 | P 1 mg 3.9 years | 6214 | 68.0 |
| CIRCLE [29] | Retrospective | AMI | P 2 mg 27 months | 180 | 66.6 | Pr 10 mg 39 months<br>At 10 mg 26 months<br>No statin 19 months | 151<br>161<br>251 | 68.7<br>68.4<br>71.4 |
| LAMIS [30] | Prospective; open | AMI | P 2 mg 1 years | 901 | 61.4 | | | |
| Takashima H [31] | Observational | CAD -ACS | P 2 mg 6 months | 41 | 65.1 | Diet | 41 | 65.1 |
| Toi T [32] | Prospective Randomized | ACS/AMI | P 2 mg 2–3 weeks | 80 | 62.3 | At 10 mg 2–3 weeks | 80 | 61.7 |
| JAPAN ACS [33] | Prospective, randomized, open,blind enpoit | ACS | P 4 mg 9.6 months | 125 | 62.5 | At 20 mg 9.6 months | 127 | 62.4 |
| TRUTH [34] | Prospective, open-labeled, randomized, multicenter trial | Stable and unstable CAD | P 4 mg 8 months | 58 | 65.5 | Pr 20 mg 8 months | 61 | 67.0 |
| Matsushita K [36] | Prospective, randomized | ACS | P 4 mg 10 months | 26 | 62.8 | At 20 mg<br>Pr 10 mg<br>Fluv 30 mg 10 months | 26<br>25<br>25 | 62.4<br>63.6<br>62.4 |
| TOGETHAR [40] | Prospective, open | CAD | P 2 mg 52 weeks | 46 | 62.5 | | | |
| Hattori K [42] | Prospective, open | Stable CAD | P 4 mg 9 months | 26 | 66 | Diet 9 months | 16 | 68 |
| ESCORT [53] | Prospective, randomized | ACS | P 4 mg before PCI 36 weeks | 25 | 66 | P 4 mg after 3 weeks 36 weeks | 28 | 66 |
| Hong YJ [60] | Prospective, online registry | AMI | P 2 mg 1 year | 496 | 61.4 | P 4 mg 1 year | 482 | 60.7 |

(30 mg/day). Most of the data available with pitavastatin and reported in our review have been obtained in Asian population.

## 2 Piatavastatin: Primary and Secondary Cardiovascular Prevention

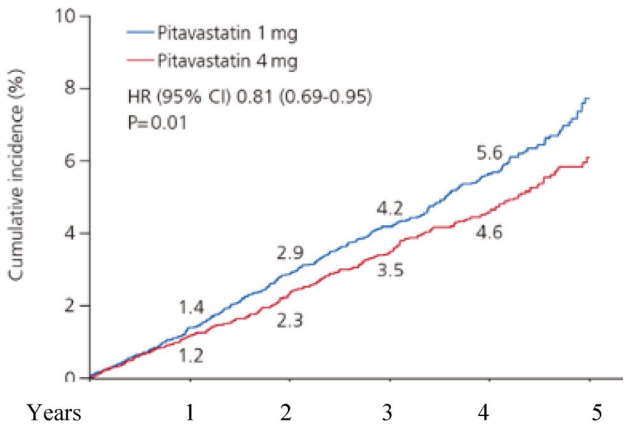
In primary cardiovascular prevention, pitavastatin has been compared with atorvastatin in the TOHO-LIP, a multicenter open trial, with blinded endpoints [23]. This study included mainly patients (75.3%) with hypercholesterolemia and concomitant high cardiovascular risk factors (advanced age, diabetes, hypertension). The cumulative 5-year incidence of the primary endpoint (composite of cardiovascular death, sudden death, acute myocardial infarction, ischemic stroke, transient ischemic attack, or heart failure) was significantly lower in pitavastatin than in atorvastatin group (2.9% vs 8.1%, $p = 0.006$). Particularly repeated coronary revascularization, in non-culprit lesion, for stable angina, was needed in 4.5% and in 12.9%, ($p < 0.001$) of patients assigned to pitavastatin and atorvastatin respectively.




From ref 23

Several trials have also investigated the efficacy of pitavastatin in secondary cardiovascular prevention, in patients with stable coronary artery disease or with ACS.

The REAL-CAD [28], a multicenter, prospective study, with blinded end points, randomized 13,054 patients with stable coronary artery disease (CAD), either to 1 mg/day or 4 mg/day of pitavastatin for an average of 3.9 years. The primary end point was a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal ischemic stroke, or unstable angina, while the secondary end point also included coronary revascularization. Differently from the low dose, the high-dose of pitavastatin, significantly improved the cumulative incidence of the primary (4.6% vs 5.6%; $p = 0.01$) and secondary end point (8.5% vs 10.4%; $p = 0.002$). A significantly more cardiovascular relative risk reduction (RRR) was obtained in patients with diabetes (− 25%), or aged < 65 years (− 33%).

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Differently from these studies that have been performed in patients at high cardiovascular risk or with stable coronary disease, the CIRCLE and LAMIS trials [29, 30] evaluated patients with acute myocardial infarct (AMI), undergoing percutaneous coronary intervention (PCI).

The CIRCLE study [29], compared pitavastatin, with pravastatin, atorvastatin and no statin (control group). After 70 months of treatment, the rate of MACE occurred in 8.3%, of patients treated with pitavastatin, in 27.2%, 19.3% and 35.1% of subjects assigned to pravastatin, atorvastatin and control group, respectively ($p < 0.001$). Multivariate analysis, after adjusting for different clinical factors, revealed that, compared with the controls, the relative risk of cardiovascular events was reduced by 51% with pitavastatin, by 21% and 27% with pravastatin and atorvastatin ($p < 0.001$). Particularly pitavastatin, differently from the other statins, significantly decreased the rate of recurrent PCI, in both, new coronary lesions (4.4% vs 12.6% and 9.9% $p = 0.003$) and target lesion (3.3% vs 12.6% and 7.5%, $p < 0.01$). The low rate of MACE observed in the CIRCLE study [29] has been confirmed by the LAMIS trial (7.3%), performed in patients with AMI, treated with pitavastatin before revascularization and followed for 12 months [30].

Overall these findings clearly demonstrate a significant benefit of pitavastatin (2–4 mg/day), in reducing the rate of major cardiovascular events, in patients at high risk for atherosclerotic disease and in those with stable CAD, or recent AMI.

## 3 Pitavastatin: Effect on Quantitative and Qualitative Aspects of Atherosclerotic Plaque

Many studies, carried out in patients with ACS or stable coronary artery disease, have evaluated the changes induced by pitavastatin on quantitative and qualitative aspects of non-culprit coronary atherosclerotic plaque, using a variety of intracoronary imaging techniques, [Intravascular ultrasound (IVUS), virtual histology intravascular ultrasound (VH-IVUS), integrated backscatter intravascular ultrasound (IB-IVUS), angioscopy or optical coherence tomography (OCT)].

These effects have been investigated in comparison with placebo [31], atorvastatin [32–34], pravastatin [34, 35] and fluvastatin [34], as well in open-label trials.

In a trial performed in patients with scheduled or primary PCI [31], pitavastatin administered within 48 h from revascularization, significantly lowered by 10,6% plaque volume index that, instead, was increased by 8.1% in the placebo group ($p < 0.001$).

Similar effect has been obtained comparing pitavastatin with atorvastatin [32] in patients with ACS. Patients

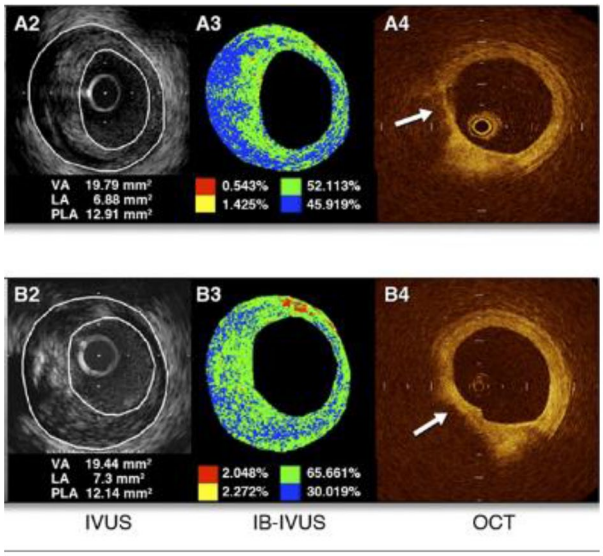
treated with pitavastatin showed a significantly reduction of atheroma volume index (− 2.6%, p < 0.001), which instead increased by + 0.2% in atorvastatin treated subjects. It is noteworthy that this result was achieved after a very short time of statins treatment (2–3 weeks) and, particularly, in patients with dense calcium plaque ratios < 10%.

Conversely in the JAPAN-ACS [33], atorvastatin and pitavastatin, started within 72 h after successful revascularization, led to a similar changes in coronary plaque volume, (pitavastatin − 16.9%, atorvastatin − 18.1%, p = 0.5), indicating a non-inferiority of pitavastatin, compared with atorvastatin**.**

Further beneficial effects of pitavastatin have been evaluated using virtual histology intravascular ultrasound (VH-IVUS), a method for accurate analysis of coronary atherosclerotic plaques composition. In patients with angina pectoris [34, 35], pitavastatin, differently from pravastatin, decreased coronary plaque volume index (− 5.0% vs + 1.1%) and the amount of fibro-fatty component (− 25.7% vs − 20.9%). This finding has also been obtained in the YOKOHAMA-ACS study performed in patients with ACS [36], treated 72 h after revascularization. At 10 months follow-up, atheroma volume was significantly lowered in pitavastatin, but not in pravastatin (− 8.1% vs + 0.4%) and also in fluvastatin (30 mg/day) treated patients (+ 3.1%), while the effect of pitavastatin and atorvastatin were comparable (− 8.1% and − 11.1%). However the dose of fluvastatin in this study have been very low, because high dose (60 mg/day) has been reported to be associated with a significant regression of plaque volume [37].

Angioscopy is an interesting tool to detect the lipid core of coronary atherosclerosis [8, 38, 39]. This imaging modality has been used in the TOGETHAR [40] trial, that assessed the effectiveness of pitavastatin in coronary plaques with large lipid core (yellow grade ≥ 2). After 52 weeks of treatment yellow grade intensity was significantly lowered from 2.9 to 2.6, (p < 0.04), and was correlated with the maximum yellow grade at baseline. Therefore, by decreasing yellow grade, pitavastatin stabilized coronary plaque vulnerability, given the negative relationship between high lipid-rich core and fibrous cap thickness [8, 41].

A complete overview of atheroma changes induced by pitavastatin has been evaluated in a study that used, in the same patients and simultaneously, angiography, serial optical coherence tomography (OCT), grayscale IVUS and integrated backscatter-IVUS imaging [42]. Patients with stable CAD, undergoing elective PCI, were treated with pitavastatin or with diet (control group) for 9 months. Differently from controls, pitavastatin significantly decreased plaque volume and lipid volume indexes (− 6.5%, p = 0.03 and − 6.7%, p = 0.02 respectively) and significantly increased by 35% (p = 0.001) fibrous cap thickness.




Plaque volume index (A2 and B2). Lipid volume index and fibrous volume index (A3 and B3). Fibrous cap thickness (arrows in A4 and B4).
From ref 42

Coronary Angiographic, Grayscale IVUS, IB-IVUS, and OCT at Baseline (A) and at Follow-Up (B)

Taken all together, the results of these studies highlight that pitavastatin (2–4 mg/day) decreases the incidence of MACE in primary and secondary prevention, suppresses atherosclerotic plaques progression and leads to stabilization of vulnerable plaques, an important hallmark correlated with reduced risk of acute cardiovascular events [10, 11, 13–15].

## 4 Potential Pharmacological Mechanism Involved in the Effects on Coronary Plaques

While the favourable effect of statins, in primary and secondary cardiovascular prevention, is well documented, the mechanism by which statins slow the progression of coronary atherosclerotic lesions and, particularly, modify atheroma components, is not precisely understood [19, 20]. However there is evidence that patients with ACS, treated with statins, before PCI, have an improvement of cardiovascular outcomes [43–45]. Likewise, it has been shown, that the risk of PCI-related peri-procedural complications and MACE [20, 46–48] can be significantly prevented by statins preloading, (before PCI), both in patients with ACS or with stable coronary artery disease [1, 49–51]. The cardiovascular protection of statins pretreatment, both in subjects already in treatment or in naïve-statins patients, does not appear to be due to the significant reduction of plasma lipids levels, but rather to two differential time-related effects, on

one side an early increase of fibrous cap thickness and on the other the reduction of coronary plaque volume [19, 44, 52].

The effect of early statin therapy on the atheroma components has been highlighted by the ESCORT study [53], performed in two groups of patients with ACS, which started pitavastatin either within 24 h (early statin group), of intravascular optical coherence tomography (OCT), or 3 weeks after (late statin group). After 3 weeks, minimum fibrous-cap thickness was significantly greater only in the early treated group (+ 20 µm, $p < 0.05$), while this parameter was decreased in the late treated group, (− 5 µm, $p < 0.05$), without any change on plaque lipid volume in both groups. Conversely, after a long period (36 months), fibrous-cap thickness significantly increased further, while plaque lipid volume significantly decreased in all patients. Therefore pitavastatin, after a short period, increased only fibrous-cap thickness, lowering plaque vulnerability, while after a long period it also decreased plaque volume. These results confirm the finding of a previous study which has shown an increase in fibrous-cap thickness with simultaneously, angiography, serial optical coherence tomography (OCT), gray-scale IVUS and integrated backscatter-IVUS imaging [42].

The potential pharmacological mechanism for the early impact of statins on atherosclerotic plaque vulnerability, might be related, besides the lipid-lowering, with the so-called "pleitropic effects" [54] and, particularly, with the antithrombotic and anti-inflammatory properties [50, 55].

Pitavastatin, has been reported, improves endothelial function, decreases some markers of platelet activation, reduces oxidative stress and modulates vascular inflammatory pathway [23, 56]. These effects have been evaluated in "vitro" [57], in animal models [58], as well in patients with atherosclerotic lesions [59].

## 5 Appropriate Dosage

The dosage of pitavastatin in cardiovascular prevention deserves some comments. Although, in most studies, high dose (4 mg/day), significantly protected patients from recurrent cardiovascular events, the LAMIS II trial [60], performed in subjects with AMI, did not show significant difference between 2 and 4 mg/day of pitavastatin. The primary efficacy endpoint (composite of cardiac death, nonfatal myocardial infarction, target-lesion revascularization, hospitalization for unstable angina, heart failure or arrhythmic events) and the secondary efficacy endpoint (target vessel revascularization + MACE) occurred in 9.1–9.1% and in 9.5–9.8% respectively, confirming the results of LAMIS, TOGETHAR and TOHO-LIP studies [23, 29, 30, 40]. However, as the lipids lowering of pitavastatin is dose dependent [61, 62], 4 mg/day, would be the suitable dosage for secondary CV prevention, as reported, particularly in the REAL-CAD and ESCORT trials [28].

## 6 Cost-Effectiveness

There are several reports that support the cost-effectiveness of pitavastatin treatment, although this item may be a minor problem since the drug is available as generic in an increasing number of countries all over the world. Jeong et al. [63] performed a comparison of the cost-effectiveness of statins according to the baseline low-density lipoprotein cholesterol level in Korea: cost of pitavastatin was lower than pravastatina, atorvastatin or simvastatin after getting the same LDL cholesterol reduction. Sansanayudh et al. [64] Comparative Efficacy and Safety of Low-Dose Pitavastatin Versus Atorvastatin in Patients with Hypercholesterolemia. Pitavastatin 1 mg once daily was associated with very low monthly cost per percent LDL-C reduction ($0.77) compared with atorvastatin 10 mg once daily ($1.56).

## 7 Conclusions

Our review, the first, to our knowledge on this topic, provides the evidence that pitavastatin decreases the rate of cardiovascular outcomes, in primary and secondary cardiovascular prevention, both in patients with ACS or stable CAD. Moreover the impact of pitavastatin on atheroma volume and composition has been demonstrated in several studies by using different methods of imaging. Globally the effectiveness of pitavastatin is better or not inferior to that of other statins. The 2019 ESC/EAS guidelines [1] consider pitavastatin, together with rosuvastatin and atorvastatin, a suitable choice, for cardiovascular prevention in patients with dyslipidemia, particularly for the absence of metabolic drug–drug interactions. Moreover early therapy with pitavastatin in patients with ACS increases fibrous-cap thickness and decreases the volume and lipid content of vulnerable coronary lesions. This aspect is underlined by the ESC/EAS guidelines [1], which recommend to initiate soon statin treatment, before PCI, in patients with ACS, to lower the risk of peri-procedural or future MACE. The beneficial effect of statins in patients with CAD is the result on one side of the lipids lowering activity and on the other of the cholesterol-independend "pleiotropic effects". Cardiologists can consider pitavastatin as an alternative therapeutic choice, bearing in mind the cost-effectiveness, in comparison with other statins with similar efficacy.

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