

Effects of Statin Treatment on Patients with Angina and Normal or Nearly Normal Angiograms

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Abstract

This article offers an updated and comprehensive overview of major findings on the effects of statin treatment in patients with chronic angina but without any epicardial coronary artery with obstructive lesion.

Keywords

Statins, non-obstructive coronary artery disease, cardiac syndrome X, coronary microvascular dysfunction, vasospastic angina

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Statins are commonly used in patients with hypercholesterolaemia and in those with cardiovascular diseases – that is, peripheral artery disease and coronary artery disease (CAD) – for the prevention of atheromatous plaque development, progression and complications, with the aim of reducing subsequent major adverse cardiovascular events (MACE), i.e. cardiac death, acute MI, stroke and heart failure.

The beneficial role of these drugs is partially driven by their lipid-lowering effect but is also due to their pleiotropic effects on the molecular pathways involved in inflammation and oxidative stress.^{1,2} Statins reduce NADPH-oxidase activity and subunit isoprenylation as well as promoting endothelial nitric oxide synthase activity directly and via the induction of tetrahydrobiopterin synthesis, effects that seem to be reversed by the addition of mevalonate, a product of beta-hydroxy beta-methylglutaryl-coenzyme A reductase.³⁻⁸

The molecular actions statins have on inflammation and endothelial function have resulted in several studies investigating their use in patients with chest pain/discomfort and normal or slightly abnormal coronary arteriograms. These patients have a poor quality of life and recent analyses have shown their prognosis is not so benign as previously thought.⁹⁻¹⁶ Patients with angina (i.e. chest pain/discomfort) and non-obstructive CAD (1–49% lumen stenosis) are at increased risk for MACE compared with the asymptomatic population.^{13,16} With the widespread use of coronary angiography and other imaging techniques, there is increasing evidence that, even among those with acute coronary syndrome, the proportion of the patients at increased risk of MACE is greater than originally thought.¹³⁻¹⁸

This article provides a comprehensive overview of major findings on the effects of statin treatment in patients with chronic angina and epicardial coronary arteries without obstructive (>50%) lumen stenosis.

Effect of Statin Therapy on 'Soft' Endpoints

Several small observational studies and randomised clinical trials have evaluated the effects of statin treatment on the occurrence of angina, exercise capacity, endothelial function and coronary flow reserve (CFR).

Initial studies in the late 1990s analysed the effect of statins in patients with non-obstructive CAD and hypercholesterolaemia.^{19,20} In 1999, Baller et al. enrolled 23 patients (five women) with angina, normal or slightly abnormal angiograms (the latter defined as the presence of $\leq 30\%$ stenosis) and LDL cholesterol >3.89 mmol/l (mean 4.27 ± 0.8 mmol/l), analysing their myocardial blood flow before and after 6 months of lipid-lowering therapy with simvastatin. The authors found that simvastatin treatment improved participants' overall coronary vasodilator capacity in addition to lowering serum cholesterol concentration. In fact, treatment resulted in an increase in CFR (from 2.2 ± 0.6 to 2.64 ± 0.6 ; $p < 0.01$) and maximal coronary flow under pharmacological stress with dipyridamole (from 182 ± 36 ml/min $\times 100$ g to 238 ± 58 ml/min $\times 100$ g; $p < 0.001$) and decreased the minimum coronary resistance (from 0.51 ± 0.12 mmHg to 0.40 ± 0.14 mmHg; $p < 0.001$). In addition to this, the symptoms of angina regressed in most patients. In light of these results, the authors concluded that intensive lipid-lowering treatment with simvastatin provided vasoprotection in patients in the early stages of coronary atherosclerosis and could potentially prevent disease progression.¹⁹

In the same year, Mansur et al. published the first randomised control study of the effect of statin therapy on positive exercise stress tests in patients with severe hypercholesterolaemia (total serum cholesterol >7.77 mmol/l) and normal coronary angiograms.²⁰ Patients with diabetes and hypertension were excluded. After 12 weeks of diet (American Heart Association step 1 diet), the 43 patients were randomly

assigned to treatment with diet alone or with diet and a statin (20 mg lovastatin daily or 10 mg simvastatin daily) for a further 16 weeks. Diet alone produced little change in cholesterol and no change in exercise resistance whereas the addition of a statin decreased total and LDL cholesterol levels and improved exercise-induced myocardial ischaemia. After 16 weeks, the number of patients that still had a positive exercise test was significantly lower in the statin group than in the diet-only group (13% versus 75%; $p=0.01$). The authors hypothesised that, since normal angiograms (smooth coronary arteries at angiography) were an inclusion criterion, the increase in exercise capacity could have been the consequence of improved coronary endothelial function secondary to the reduction in cholesterol plasma concentrations obtained with statin treatment.²⁰ This supported the theory of microvascular dysfunction as a possible cause of myocardial ischaemia and led them to introduce the concept of statins as a possible treatment for endothelial dysfunction.

Since these two pioneer investigations on the effect of statins on myocardial ischaemia in patients with non-obstructive coronary arteries, several scientists have examined the consequences of statins on coronary endothelial function through the direct assessment of myocardial perfusion and coronary flow. They have also investigated peripheral endothelial function using markers, such as brachial flow-mediated dilation (FMD), which is a surrogate of coronary endothelial function. Analysis of the effect of statin treatment has also provided some insight into the pathogenesis of cardiac syndrome X.

In the late 1990s and early 2000s, patients with angina, transient myocardial ischaemia and normal angiograms were often considered to be suffering from cardiac syndrome X (CSX).²¹⁻²³ This diagnosis underlines the fact that the causes of myocardial ischaemia were still unclear. In 2003, a single-blind, randomised, placebo-controlled study looked at the effects of statin therapy versus placebo in 40 patients with CSX.²⁴ Patients with left ventricular hypertrophy, hypertension, diabetes and LDL cholesterol ≥ 4.15 mmol/l were excluded from the study. At baseline, FMD was significantly impaired in all patients; however, after 3 months FMD had significantly improved in the pravastatin group ($9.7 \pm 8.6\%$ versus $16.3 \pm 6.8\%$, $p=0.006$) but there was no significant change in the placebo group ($9.0 \pm 7.9\%$ versus $8.8 \pm 5.5\%$, $p=0.35$). There were also significant improvements in the time needed for 1 mm ST-segment depression (from 267 ± 105 seconds to 419 ± 162 seconds; $p=0.001$) and total duration of exercise (from 530 ± 162 seconds to 585 ± 165 seconds; $p=0.001$) and an improvement in the Canadian Cardiovascular Society Angina grading scale in the pravastatin group but not the placebo group. It is interesting to note that a moderate association between changes in FMD and time to 1 mm ST-segment depression was observed ($r=0.525$, $p=0.04$), suggesting an underlying relationship between endothelial function and myocardial ischaemia.²⁴

Houghton et al. assessed the effects that cholesterol lowering with a statin had on coronary resistance in a small observational study of six patients with a history of chest pain and normal angiograms.²⁵ This study deserves to be mentioned because it provided important insight into the possible mechanisms of myocardial ischaemia in patients with normal epicardial coronary arteries. Coronary endothelium-independent and dependent vasodilatation were examined using intracoronary administration of adenosine and acetylcholine, respectively, and coronary blood flow was measured with an intracoronary flow Doppler wire. After 6 months of 20 mg pravastatin daily, the authors found no

significant differences in adenosine-mediated increase in coronary blood flow compared to baseline (i.e. there were no changes in endothelium-independent vasodilation) but a significant difference in acetylcholine infusion peak (endothelium-dependent vasodilation), which rose from $97 \pm 13\%$ to $160 \pm 16\%$ ($p=0.01$). There was also a strong correlation ($r=-0.87$, $p=0.02$) between improvement in coronary flow reserve (CFR) and reduction in LDL cholesterol, suggesting that endothelial function may depend upon circulating lipid profiles, among other factors.²⁵ In conclusion, the study proved that endothelial function was significantly improved with pravastatin.

Soon after this, another prospective single-blind study provided further insight into the benefits of statin treatment and added to our understanding of the pathophysiology of myocardial ischaemia in patients with normal angiograms.²⁶ Pizzi et al. examined the effects of atorvastatin 40 mg per day plus ramipril 10 mg per day versus placebo in 45 patients with CSX. After 6 months, patients in the intervention group had fewer episodes of chest pain (4.4 ± 2.9 versus 9.2 ± 2.7 episodes per month; $p=0.004$), improved time to peak exercise (from 450 ± 82.2 seconds to 555.3 ± 84.6 seconds, $p=0.045$) and significantly increased FMD (from $2.2 \pm 1.3\%$ to $4.2 \pm 1.7\%$; $p=0.001$), while there were no significant changes in the placebo group. The authors found a significant correlation between FMD and time to peak exercise ($r=0.29$; $p<0.01$), reinforcing the notion that endothelial function may be the underlying cause of ischaemia in these patients. Moreover, in the dual-therapy group, the levels of superoxide dismutase – which is one of the major antioxidant enzymes of the vessel wall – decreased from 268.4 ± 53.7 U/ml to 188.1 ± 29.6 U/ml during follow-up ($p<0.001$). The levels of this enzyme had a negative correlation with changes in FMD ($r=0.38$; $p=0.01$), exercise capacity ($r=0.22$; $p=0.03$) and Seattle Angina Questionnaire score ($r=0.46$; $p<0.01$), suggesting that in patients with CSX, the benefit of dual therapy may be related to a reduction in oxidative stress.²⁶ Unfortunately, since the treatment group received both an angiotensin-converting enzyme inhibitor and a statin, the authors were unable to determine whether both or only one of the drugs was responsible for the beneficial effects.

Fábián et al. studied the effects of statins on endothelial function and exercise-induced ischaemia in 40 CSX patients randomised to 20 mg simvastatin per day or placebo for 3 months.²⁷ Similar to previous studies, simvastatin reduced total cholesterol, improved brachial FMD (from $4.01 \pm 0.91\%$ to $6.12 \pm 0.79\%$; $p<0.0001$) and time to 1 mm ST segment depression (from 4.45 ± 0.39 minutes to 5.33 ± 0.27 minutes; $p<0.0001$) in comparison to placebo.

Zhang et al. reported on the effects of 3 months of treatment on 68 CSX patients randomised to a statin, a calcium-channel blocker or dual therapy (statin plus calcium-channel blocker).²⁸ All three groups showed significant ($p<0.05$) improvements in CFR (fluvastatin +23.2% versus diltiazem +12.4% versus fluvastatin–diltiazem +29.1%) and time to ST segment depression (fluvastatin from 241 ± 97 seconds to 410 ± 140 seconds; diltiazem from 258 ± 91 seconds to 392 ± 124 seconds; fluvastatin–diltiazem from 250 ± 104 seconds to 446 ± 164 seconds). The greatest improvements were recorded in the fluvastatin and dual therapy groups, suggesting the statin had played a dominant role.²⁸ Remarkably, a significant increase in nitric oxide and reduction in endothelin-1 was observed in the two groups receiving statins, indicating that the pleiotropic effects of this drug are fundamental for improved coronary endothelial function in patients with normal angiograms.

A more recent double-blind, placebo-controlled clinical trial randomised 58 patients (40 women and 18 men) with angina pectoris, evidence of inducible ischaemia, non-obstructive CAD (<50% lumen stenosis) and normal total cholesterolaemia (<8 mmol/l) to atorvastatin 20 mg per day or placebo for 6 months to determine the effect of atorvastatin on endothelial function.²⁹ A significant improvement in brachial FMD among patients in the statin group (although FMD never met the criteria for normal endothelial function) but no change in the placebo group at 3- and 6-month follow-up was observed, demonstrating that even moderate doses of atorvastatin improve the endothelial function of peripheral arteries in patients with normal serum total cholesterol, inducible myocardial ischaemia and non-obstructive CAD.

Further insights into the role of statins in coronary circulation were elucidated by Caliskan et al., who explored the effect of 20 mg atorvastatin per day in 20 patients with normal epicardial angiograms but slow coronary flow (i.e. late coronary opacification during angiography, defined as corrected thrombolysis in MI frame count >2 standard deviations from the normal published range).³⁰ Previous acute MI was an exclusion criterion in this study. CFR, using transthoracic Doppler echocardiography, was evaluated at baseline and after 8 weeks of statin treatment. At follow-up, the authors observed significant increases in CFR (from 1.95 ± 0.38 to 2.54 ± 0.56 , $p < 0.001$) and hyperaemic diastolic peak flow velocity (from 45.4 ± 12.7 cm/s to 53.0 ± 15.8 cm/s, $p = 0.01$) and a significant decrease in diastolic peak flow velocity (from 23.3 ± 5.6 cm/s to 20.7 ± 3.5 cm/s, $p = 0.02$) in atorvastatin-treated patients, demonstrating that statin therapy significantly improves the microvascular function of patients with normal angiograms and slow coronary flow.³⁰

Ulus et al. investigated the effects of statins on myocardial perfusion in patients with metabolic syndrome.³¹ At 6 months they found that, in patients with a myocardial perfusion defect on exercise stress technetium-99m single-photon emission CT and normal coronary arteries, 20 mg per day of atorvastatin significantly improved myocardial perfusion ($p < 0.01$), as measured by summed stress score, summed rest score and summed difference score.

In summary, several small observational and randomised trials have shown that statin treatment has beneficial effects in patients with angina and non-obstructive coronary angiograms (with or without hypercholesterolaemia).^{19,20,24-31} These effects include improvements in endothelial and microvascular function, exercise capacity and myocardial perfusion, as well as a reduction in or regression of angina symptoms.^{19,20,24-31}

Effect of Statin Therapy on 'Hard' Endpoints

Several large observational studies designed to evaluate the effects of statins on 'hard' endpoints in non-obstructive CAD patients have been carried out in recent years.

Results from the COroNary CT Angiography Evaluation for Clinical Outcomes (CONFIRM) registry provided evidence of an association between the presence and extent of non-obstructive CAD and mortality.³² Chow et al. identified 10,418 patients with stable CAD and normal coronary arteries ($n = 5,712$) or non-obstructive CAD (1–49% lumen stenosis, $n = 4,706$) using coronary CT angiography (CCTA).

Patients with non-obstructive CAD were more likely to be taking statins (43.2% versus 25.1%; $p < 0.001$) and aspirin (46.2% versus 30.8%; $p < 0.001$) at the time of CCTA when compared with patients with normal angiograms. After a median follow-up period of 27.2 months, statin therapy was associated with a significant improvement in survival in non-obstructive CAD patients (HR 0.45; 95% CI [0.27–0.75]), but not in patients with normal angiograms (HR 0.66; 95% CI [0.30–1.43]).³² No information was collected on the initiation or discontinuation of statin therapy after CCTA, thus patients with normal arteries may have discontinued statin therapy, thereby underestimating the benefit of statins in this subpopulation.

Hwang et al. identified a cohort of 8,372 subjects with non-obstructive CAD (1–49% lumen stenosis) who were not on statin therapy from among 47,708 consecutive individuals who underwent CCTA for evaluation of CAD.³³ Of the individuals with non-obstructive CAD, 1,983 started statin therapy while 6,389 did not. After a median follow-up of 27.6 months, statin use was associated with a significant reduction in all-cause mortality (HR 0.397; 95% CI [0.26–0.60]) and the composite of mortality and late coronary revascularisation (HR 0.43; 95% CI [0.31–0.60]). This association remained regardless of other factors, including age, sex, the presence of hypertension or diabetes, level of LDL cholesterol or C-reactive protein, coronary artery calcium score or glomerular filtration rate.

In summary, two observational studies including a total of >18,700 patients with non-obstructive CAD have shown that statin use is associated with a significant reduction in all-cause mortality during a follow-up period of approximately 2.5 years.^{32,33} However, since these studies were not randomised trials, the results should be accepted with caution as they may have been influenced by patient selection.

Conclusion

A number of studies exploring the effects of statin treatment on soft endpoints actually had pathophysiological endpoints that have helped us understand the causes of ischaemia in patients with non-obstructive CAD.^{19,20,24-31} It is currently recognised that myocardial ischaemia in these individuals is often the consequence of reduced coronary microvascular dilatory responses and increased coronary resistance due to endothelial dysfunction and/or vasomotor disorder (involving the microvascular and/or epicardial bed).³⁴

Studies in patients with angina and non-obstructive CAD show that statins increase myocardial perfusion and improve symptoms in subjects with mild coronary atherosclerosis and even in those with normal angiograms.^{19,24,26,29} Current international guidelines suggest statin treatment for all patients with chronic coronary syndrome, including those with microvascular angina.³⁴

Finally, preliminary data have shown that statin treatment improves survival in patients with mild coronary atherosclerosis (1–49% lumen stenosis) but not in those with normal angiograms (0% lumen stenosis).^{32,33} However, since patient enrolment in these studies was not randomised, further research (i.e. adequately powered randomised trials) is needed to clarify the protective role of statins on clinical outcomes in patients with chronic coronary syndrome without obstructive CAD. ■

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