

# Pharmacologic prevention of coronary plaque rupture – the major cause of acute coronary syndromes

Petri T. Kovanen and Markku O. Pentikäinen  
Wihuri Research Institute, Helsinki, Finland

Correspondence: Petri T. Kovanen, Wihuri Research Institute, Kallioliinantie 4, 00140 Helsinki, Finland.  
Tel: +358 9 681 4131; fax: +358 9 637 476; e-mail: petri.kovanen@wri.fi

## Abstract

The rupture of a vulnerable coronary atherosclerotic plaque results in coronary thrombosis, the main cause of unstable angina, acute myocardial infarction, and sudden cardiac death. Usually, a culprit plaque that ultimately ruptures does not cause significant flow-limiting stenosis, but is characterized by a typical histological structure: it contains a large necrotic lipid core and a thin fibrous cap, which separates the core from the circulating blood. The formation of such thin-cap fibroatheromata results from a reactive inflammatory response of the growing plaque to continuous accumulation of lipids derived from low-density lipoprotein. Consequently, adequate control of both lipid accumulation and inflammation in the plaque are crucial in the prevention of plaque rupture. At present, these requirements are pharmacologically best fulfilled by statins. Emerging therapies with a similar dual effect on coronary plaques include intravenous infusion of synthetic high-density lipoprotein. These therapies are likely initially to stabilize inflamed plaques and, if administered sufficiently rigorously and for a sufficiently long time, they lead to regression of lipid-laden vulnerable plaques. It is becoming increasingly evident that other cardiovascular drugs may also increase plaque stability. These agents include peroxisome proliferator activated receptor  $\alpha$  and  $\gamma$  agonists, angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, calcium channel blockers, and aspirin.

■ *Heart Metab.* 2007;36:9–14.

**Keywords:** Coronary artery disease, plaque rupture, pharmacotherapy

## Introduction

Atherosclerosis of epicardial coronary arteries and their major branches is the underlying cause of ischemic coronary heart disease. Acute coronary syndrome usually results from an occluding thrombus of the culprit coronary artery and manifests clinically as unstable angina, acute myocardial infarction, or sudden cardiac death. The most common cause of acute coronary thrombosis is plaque rupture, notably the rupture of a thin-cap fibroatheroma [1]. Careful analysis of such ruptured culprit lesions has created the concept of “vulnerable plaques”. These plaques typically cause only minor stenosis of the coronary lumen and are morphologically characterized by a

large lipid core and a thin cap, which contains few collagen-producing smooth muscle cells but numerous inflammatory cells, namely macrophages, T cells, and mast cells [2].

Ambrose and D’Agate recently discussed the systemic therapies that prevent acute myocardial infarction by potentially stabilizing vulnerable plaques [3]. Since then, new clinical studies, new imaging techniques, and direct analysis of excised atherosclerotic lesions after defined drug therapies have provided new insight into pharmacological plaque stabilization. Here, we briefly discuss some of these new findings and their implications for pharmacological stabilization of vulnerable coronary plaques. The findings are summarized in *Table 1*.

# Main clinical article

Petri T. Kovanen and Markku O. Pentikäinen

Table 1. Clinical and biological effects of drugs used to treat cardiometabolic diseases

Drug	Prevention of cardiovascular events	Plaque stabilization based on plaque composition	Retardation of coronary or carotid lesion progression	Inhibition of experimental atherogenesis
Statins	+	+	+	+
Synthetic HDL			+	+
ACE inhibitors/AIIR blockers	+	+	+	+
Fibrates	+		+	+
Thiazolidinediones	+	+	+	+
Calcium channel blockers	+		+	+
$\beta$ -Blockers	+		+	+
Aspirin	+			+

ACE, angiotensin-converting enzyme; AIIR, angiotensin II receptor; HDL, high-density lipoprotein.

## Statins

There is extensive evidence to indicate that inhibition of the rate-regulating enzyme of cholesterol biosynthesis, 3-hydroxy-3-methylglutaryl coenzyme A reductase, by means of vastatin drugs ("statins") reduces the incidence of acute coronary syndrome in the settings of both primary and secondary prevention. Experimental studies with cultured cells and animal models have provided compelling evidence that statins diminish inflammation in the arterial wall and may thereby contribute to the stabilization of vulnerable plaques. Most importantly, this conclusion also appears to apply to humans, notably to patients with advanced atherosclerosis. Thus immunohistochemical analyses of atherosclerotic coronary and carotid samples surgically removed from patients who have been treated with statins have shown that these drugs are able to decrease inflammation and to promote the transformation of vulnerable plaques into more stable plaques [4–6]. On the basis of these findings, we can conclude that any successful prevention of coronary or carotid atherothrombotic events by statin medication is likely to result from plaque stabilization.

The above conclusion is supported by the clinical findings of the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 (PROVE-IT–TIMI 22) trial, in which high-dose atorvastatin (80 mg/day) initiated early after acute coronary syndrome, compared with standard-dose pravastatin (40 mg/day), led to a rapid reduction in clinical events [7]. This effect was seen within 1 month after the initiation of the treatment. In this study, the patients who achieved the lowest low-density lipoprotein (LDL) cholesterol and C-reactive protein (CRP) concentrations at 30 days also had the lowest risk of future acute cardiac events. The early benefits of statin therapy correlated with CRP reduction, which may have been related to the intensity of the direct anti-inflammatory plaque-stabilizing or "pleiotropic" effects of the statins. Further support for such plaque-stabilizing effects

of statins, which are independent of their lipid-decreasing ability, was obtained in the Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) study, which compared the effects of the above-mentioned two statin regimens on the progression of change in coronary atheroma volume [8]. Intravascular ultrasound revealed that, relative to a given reduction in LDL cholesterol concentration, the rate of progression of atheroma was slower in individuals receiving atorvastatin than in those receiving pravastatin. The notably greater reduction of CRP in the atorvastatin group (36% compared with 5%) seemed to explain at least some of this additional benefit. It must be noted, however, that high LDL cholesterol concentrations are proinflammatory per se, and that the reduction of LDL cholesterol by means other than statins, for example by physically removing LDL particles from the circulation (LDL apheresis), also exerts anti-inflammatory effects, as reflected by a decrease in C-reactive protein concentrations after such treatment [9]. Accordingly, the contribution of the direct pleiotropic effects of statins to their anti-inflammatory actions remains unknown.

Most recently, the A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden (ASTEROID) trial convincingly demonstrated that very intensive statin therapy (rosuvastatin 40 mg), which decreases LDL cholesterol to "physiological" concentrations (1.5 mmol/L or 60 mg/dL), can induce true regression of human advanced atherosclerosis – that is, it decreases the size of coronary atherosclerotic plaques in patients with angiographic evidence of coronary artery disease [10]. Obviously, such an aggressive lipid-decreasing strategy that reverses the atherosclerotic disease process at its very late stages inevitably also leads to plaque stabilization. Thus, in patients at very high risk of developing atherothrombotic complications in their coronary tree, LDL cholesterol concentrations should be decreased as much as possible in a safe manner. The observed simultaneous significant 15%

---

## Main clinical article

### *Pharmacologic prevention of coronary plaque rupture*

---

increase in HDL cholesterol may have contributed to the substantial reduction in the atheroma lesion burden in these patients.

#### **High-density lipoprotein infusion therapy**

High-density lipoprotein infusion therapy is a novel and emerging modality in the acute treatment of atherosclerosis. In this treatment, synthetic HDL particles containing complexes of phospholipids with either native apolipoprotein (apo) A-I or recombinant apolipoprotein (apo) A-I Milano, a variant form of native apoA-I, are repeatedly infused intravenously. Experiments with animal models have convincingly shown that induction of reverse cholesterol transport by infusion of phospholipid vesicles or either type of synthetic HDL leads to rapid mobilization of cholesterol from tissues, promotes fecal excretion of steroids, and reverses endothelial dysfunction induced by hypercholesterolemia [11]. Most importantly, after a single injection of a high dose of synthetic HDL containing apoA-I Milano, the size and macrophage content of established atherosclerotic lesions in apoE-deficient mice were significantly decreased within 48 h, reflecting regression and potential stabilization of atherosclerotic lesions [12]. Recently, two small clinical studies have evaluated the use of these compounds in patients with acute coronary syndromes. Nissen et al [13] reported that over a period of 5 weeks, weekly injections of synthetic HDL containing apoA-I Milano induced a 4.2% decrease in atheroma volume, as assessed by intravenous ultrasound. Using similar intravenous ultrasound examinations, Tardif et al [14] showed that four weekly injections of reconstituted HDL containing normal apoA-I decreased atheroma volume by 3.4%, with a concomitant change in plaque characteristics compatible with an increase in the content of dense fibrous tissue – that is, the treatment appeared to induce more stable plaque composition. Moreover, the treatment significantly decreased the mean reduction in coronary luminal diameter, as determined with quantitative coronary angiography. Overall, on the basis of experimental and clinical data, induction of reverse cholesterol transport with synthetic HDL appears a promising way to stabilize plaques. However, before this mode of treatment is ready for common use, larger studies are needed to verify the safety of these compounds and to demonstrate that the observed beneficial effect on atherosclerotic plaques will actually lead to a decrease in the incidence of adverse cardiovascular events.

#### **Peroxisome proliferator activated nuclear receptor agonists**

Peroxisome proliferator activated receptors  $\alpha$  and  $\gamma$  are members of the superfamily of nuclear receptors

that regulate both lipid and glucose homeostasis in response to fatty acids and their metabolites [15]. They are expressed by the major cell types of atherosclerotic lesions, where they have the potential for negative regulation of the transcription of proinflammatory genes. Thus their activators or agonists, notably the two classes of drugs, the fibrates and thiazolidinediones, could theoretically exert direct anti-inflammatory actions on vulnerable plaques.

Fibrates are ligands for PPAR $\alpha$  and their major lipid-regulatory effects consist of a reduction in triglycerides and an increase in HDL cholesterol. Various fibrates have been shown to decrease the incidence of acute cardiovascular events, but to do so less consistently than statins [15]. Fibrates also decrease experimental atherogenesis and diminish the size of carotid plaques, with a concomitant decrease in the incidence of strokes in patients with essential hypertension [16]. Thus fibrates appear to have some plaque-stabilizing effects. It is obvious that these effects largely result from the ability of fibrates to regulate plasma lipids; the extent of their plaque-stabilizing potential attributed to direct effects on various cell types present in vulnerable plaques remains unknown.

Thiazolidinediones are ligands for PPAR $\gamma$  and they increase insulin sensitivity and have favorable effects on blood glucose concentrations and the serum lipid profile. Moreover, thiazolidinediones have anti-inflammatory effects on cultured vascular cells and slow down the development of atherogenesis in experimental animals. In the PROactive study, pioglitazone was found to decrease cardiovascular events in patients with type 2 diabetes [17]. Moreover, both pioglitazone [18] and rosiglitazone [19] decreased carotid atherosclerosis in diabetic patients and, interestingly, rosiglitazone has been shown to inhibit inflammation and to stabilize carotid plaques in non diabetic patients [20,21]. Unfortunately, however, a recent meta-analysis of the cardiovascular effects of rosiglitazone showed that its use was associated with a significant increase in the risk of myocardial infarction, which necessitates careful reconsideration of its use in patients with cardiovascular diseases [22].

#### **Angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists**

By reducing blood pressure, angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor type 1 antagonists also reduce the physical stress exerted on vulnerable plaques and hence tend to prevent their rupture. As ACE is abundantly expressed in atherosclerotic lesions, and angiotensin II has been shown to possess potent proinflammatory effects, these compounds may also have direct effects on

plaque biology. Both ACE inhibitors and angiotensin receptor antagonists have been shown to decrease cardiovascular events in high-risk patients without heart failure [23–25]. Importantly, ultrasound imaging analysis of carotid arteries has shown that both ACE inhibitors [26] and angiotensin receptor antagonists [27] decrease the size of carotid artery atherosclerotic lesions, and treatment with irbesartan for 4 months was shown to decrease the degree of inflammation in human carotid plaques [28]. Overall, these findings suggest that inhibition of the renin–angiotensin system, both systemically and locally in lesions, helps to stabilize plaques.

## Calcium channel blockers

Dihydropyridine calcium channel blockers have been shown to have direct plaque-stabilizing effects beyond the decreasing of blood pressure, and some of these actions appear to be dependent on, and some others independent of, calcium channel modulation [29]. Earlier studies with short-acting dihydropyridine calcium channel blockers failed to show any effect on plaque size or to reduce coronary events, but more recent studies with the long-acting third-generation dihydropyridine calcium channel blockers, amlodipine and lacidipine, have shown some clinical benefit. Thus, in patients with coronary heart disease and normal blood pressure, amlodipine decreased cardiovascular morbidity and slowed down the progression of coronary and carotid atherosclerosis [30,31]. Similarly, lacidipine has been shown to inhibit the progression of carotid atherosclerosis in patients with hypertension [32].

## $\beta$ -Blockers

$\beta$ -Blockers are indicated and widely used to prevent adverse cardiovascular events after myocardial infarction. In addition, they are used in antihypertensive drug regimens. However, recent large clinical trials have challenged the use of  $\beta$ -blockers, especially atenolol, as first-line antihypertensive drugs [33].  $\beta$ -Blockers are likely to have beneficial effects on plaque biology by regulating hemodynamic forces exerted on the plaques, and so prevent cardiovascular events triggered by heavy physical exertion or psychosocial stress [34]. There is also some evidence that  $\beta$ -blockers may have antiatherogenic effects that are not mediated by their effects on hemodynamics. Thus, in experimental animals, endothelial injury caused by adrenergic stimulation can be prevented with  $\beta$ -blockers [35], and  $\beta$ -blockers have also been shown to decrease diet-induced and stress-induced atherosclerosis [36,37]. In humans,  $\beta$ -blockers have been

shown to retard the progression of carotid atherosclerosis in patients without [38] and with [39] statin medication. Overall,  $\beta$ -blockers are indicated in the primary and secondary prevention of cardiovascular diseases, and some of their beneficial effects may be derived from plaque-stabilizing effects.

## Aspirin

Aspirin, when administered in a daily single low dose (100 mg or less), is an antiplatelet agent that completely blocks the synthesis of thromboxane  $A_2$  in platelets and therefore effectively inhibits platelet-dependent formation of arterial thrombus. On the basis of this well characterized antiplatelet effect, it is easy to appreciate that low-dose aspirin is effective not only for secondary but also for primary prevention of atherothrombotic diseases [40]. Importantly, low-dose aspirin has also been demonstrated to reduce proinflammatory cytokines in patients with chronic stable angina [41]. Moreover, among apparently healthy men, aspirin was most effective in reducing the cardiovascular risk in the individuals with the most increased concentrations of C-reactive protein [42]. These findings have provided strong suggestive evidence that aspirin, besides its antiplatelet action, may have additional anti-inflammatory effects on atherosclerotic plaques. To date, this hypothesis has been tested in genetically hyperlipidemic mice, in which low-dose aspirin was found to suppress aortic inflammation and to increase the stability of already developed atherosclerotic plaques [43]. These experimental studies call for future human investigations to evaluate whether low-dose aspirin might retard the progression and evolution of human atherosclerotic plaques and prevent their conversion into vulnerable plaques.

## Conclusion

It is of major importance to realize that none of the currently available systemically applied pharmacotherapies specifically targets vulnerable coronary plaques prone to rupture. The pharmaceutical industry is actively developing molecules with this ability, and searching for the “magic bullet”. At present, decreasing LDL concentrations to physiological values and induction of true regression of lesions with statins appears to be the treatment modality closest to this ideal. In our present enthusiasm about modern medications, we should not forget the emergence of the concept of plaque stabilization [44,45]. Indeed, the formulation of this concept was prompted by the amazing results attained with “old drugs”, such as niacin and colestipol. Thus, in the Familial Atherosclerosis Treatment Study (FATS) study, a combination

# Main clinical article

## Pharmacologic prevention of coronary plaque rupture

of these two drugs induced a remarkable 80% reduction in cardiovascular events [46]. We are now witnessing the second coming of niacin along with the discovery of its receptor, and the replacement of bile acid binding resins by molecularly targeting the absorption of cholesterol from the gut with ezetimibe. We have good reason to believe that the reduction in plasma LDL cholesterol to extremely low concentrations, which is already possible today, will stabilize vulnerable plaques sufficiently to lead to a significant decrease in acute coronary events. ■

### REFERENCES

1. Virmani R, Burke AP, Farb A, Kolodgie FD. Pathology of the vulnerable plaque. *J Am Coll Cardiol*. 2006;47 (suppl 8):C13–C18.
2. Kaartinen M, van der Wal AC, van der Loos CM, et al. Mast cell infiltration in acute coronary syndromes: implications for plaque rupture. *J Am Coll Cardiol*. 1998;32:606–612.
3. Ambrose JA, D'Agate DJ. Classification of systemic therapies for potential stabilization of the vulnerable plaque to prevent acute myocardial infarction. *Am J Cardiol*. 2005;95:379–382.
4. Crisby M, Nordin-Fredriksson G, Shah PK, Yano J, Zhu J, Nilsson J. Pravastatin treatment increases collagen content and decreases lipid content, inflammation, metalloproteinases, and cell death in human carotid plaques: implications for plaque stabilization. *Circulation*. 2001;103:926–933.
5. Martin-Ventura JL, Blanco-Colio LM, Gomez-Hernandez A, et al. Intensive treatment with atorvastatin reduces inflammation in mononuclear cells and human atherosclerotic lesions in one month. *Stroke*. 2005;36:1796–1800.
6. Solem J, Levin M, Karlsson T, Grip L, Albertsson P, Wiklund O. Composition of coronary plaques obtained by directional atherectomy in stable angina: its relation to serum lipids and statin treatment. *J Intern Med*. 2006;259:267–275.
7. Ray KK, Cannon CP, McCabe CH, et al., for the PROVE IT–TIMI 22 Investigators. Early and late benefits of high-dose atorvastatin in patients with acute coronary syndromes: results from the PROVE IT–TIMI 22 trial. *J Am Coll Cardiol*. 2005;46:1405–1410.
8. Nissen SE, Tuzcu EM, Schoenhagen P, et al., for the Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) Investigators. Statin therapy, LDL cholesterol, C-reactive protein, and coronary artery disease. *N Engl J Med*. 2005;352:29–38.
9. Moriarty PM, Gibson CA, Shih J, Matias MS. C-reactive protein and other markers of inflammation among patients undergoing HELP LDL apheresis. *Atherosclerosis*. 2001;158:495–498.
10. Nissen SE, Nicholls SJ, Sipahi I, et al., for the ASTEROID Investigators. Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial. *JAMA*. 2006;295:1556–1565.
11. Newton RS, Krause BR. HDL therapy for the acute treatment of atherosclerosis. *Atheroscler Suppl*. 2002;3:31–38.
12. Shah PK, Yano J, Reyes O, et al. High-dose recombinant apolipoprotein A-I(milano) mobilizes tissue cholesterol and rapidly reduces plaque lipid and macrophage content in apolipoprotein e-deficient mice. Potential implications for acute plaque stabilization. *Circulation*. 2001;103:3047–3050.
13. Nissen SE, Tsunoda T, Tuzcu EM, et al. Effect of recombinant ApoA-I Milano on coronary atherosclerosis in patients with acute coronary syndromes: a randomized controlled trial. *JAMA*. 2003;290:2292–2300.
14. Tardif JC, Gregoire J, L'Allier PL, et al., for the Effect of rHDL on Atherosclerosis-Safety and Efficacy (ERASE) Investigators. Effects of reconstituted high-density lipoprotein infusions on coronary atherosclerosis: a randomized controlled trial. *JAMA*. 2007;297:1675–1682.
15. Gervois P, Fruchart JC, Staels B. Drug insight: mechanisms of action and therapeutic applications for agonists of peroxisome proliferator-activated receptors. *Nat Clin Pract Endocrinol Metab*. 2007;3:145–156.
16. Zhu S, Su G, Meng QH. Inhibitory effects of micronized fenofibrate on carotid atherosclerosis in patients with essential hypertension. *Clin Chem*. 2006;52:2036–2042.
17. Dormandy JA, Charbonnel B, Eckland DJ, et al., for the PROactive investigators. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAZone Clinical Trial In macroVascular Events): a randomised controlled trial. *Lancet*. 2005;366:1279–1289.
18. Langenfeld MR, Forst T, Hohberg C, et al. Pioglitazone decreases carotid intima-media thickness independently of glycemic control in patients with type 2 diabetes mellitus: results from a controlled randomized study. *Circulation*. 2005;111:2525–2531.
19. Stocker DJ, Taylor AJ, Langley RW, Jezior MR, Vigersky RA. A randomized trial of the effects of rosiglitazone and metformin on inflammation and subclinical atherosclerosis in patients with type 2 diabetes. *Am Heart J*. 2007; 153:445.e1–6.
20. Meisner F, Walcher D, Gizard F, et al. Effect of rosiglitazone treatment on plaque inflammation and collagen content in nondiabetic patients: data from a randomized placebo-controlled trial. *Arterioscler Thromb Vasc Biol*. 2006;26:845–850.
21. Marfella R, D'Amico M, Di Filippo C, et al. Increased activity of the ubiquitin–proteasome system in patients with symptomatic carotid disease is associated with enhanced inflammation and may destabilize the atherosclerotic plaque: effects of rosiglitazone treatment. *J Am Coll Cardiol*. 2006;47:2444–2455.
22. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med*. 2007;356:2457–2471.
23. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med*. 2000;342:145–153.
24. Dahlof B, Devereux RB, Kjeldsen SE, et al., for the LIFE Study Group. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet*. 2002;359:995–1003.
25. Fox KM, for the EUROpean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease Investigators. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). *Lancet*. 2003;362:782–788.
26. Lonn E, Yusuf S, Dzavik V, et al., for the SECURE Investigators. Effects of ramipril and vitamin E on atherosclerosis: the Study to Evaluate Carotid Ultrasound Changes in Patients Treated with Ramipril and Vitamin E (SECURE). *Circulation*. 2001;103:919–925.
27. Ludwig M, Stapff M, Ribeiro A, et al. Comparison of the effects of losartan and atenolol on common carotid artery intima-media thickness in patients with hypertension: results of a 2-year, double-blind, randomized, controlled study. *Clin Ther*. 2002;24:1175–1193.
28. Cipollone F, Fazia M, Iezzi A, et al. Blockade of the angiotensin II type 1 receptor stabilizes atherosclerotic plaques in humans by inhibiting prostaglandin E2-dependent matrix metalloproteinase activity. *Circulation*. 2004;109:1482–1488.
29. Mason RP. Mechanisms of plaque stabilization for the dihydropyridine calcium channel blocker amlodipine: review of the evidence. *Atherosclerosis*. 2002;165:191–199.
30. Nissen SE, Tuzcu EM, Libby P, et al., for the CAMELOT Investigators. Effect of antihypertensive agents on cardiovascular events in patients with coronary disease and normal blood pressure: the CAMELOT study: a randomized controlled trial. *JAMA*. 2004;292:2217–2225.
31. Pitt B, Byington RP, Furberg CD, et al. Effect of amlodipine on the progression of atherosclerosis and the occurrence of clinical events. PREVENT Investigators. *Circulation*. 2000;102:1503–1510.
32. Zanchetti A, Bond MG, Hennig M, et al. for the European Lacidipine Study on Atherosclerosis investigators. Calcium antagonist lacidipine slows down progression of asymptomatic carotid atherosclerosis: principal results of the European Lacidipine Study on Atherosclerosis (ELSA), a randomized, double-blind, long-term trial. *Circulation*. 2002;106:2422–24427.

---

## Main clinical article

Petri T. Kovanen and Markku O. Pentikäinen

---

33. Ong HT. Beta blockers in hypertension and cardiovascular disease. *BMJ*. 2007;334:946–949.
34. Tofler GH, Muller JE. Triggering of acute cardiovascular disease and potential preventive strategies. *Circulation*. 2006;114:1863–1872.
35. Pettersson K, Bejne B, Bjork H, Strawn WB, Bondjers G. Experimental sympathetic activation causes endothelial injury in the rabbit thoracic aorta via beta 1-adrenoceptor activation. *Circ Res*. 1990;67:1027–1034.
36. Östlund-Lindqvist AM, Lindqvist P, Brautigam J, Olsson G, Bondjers G, Nordborg C. Effect of metoprolol on diet-induced atherosclerosis in rabbits. *Arteriosclerosis*. 1988;8:40–45.
37. Kaplan JR, Manuck SB, Adams MR, Weingand KW, Clarkson TB. Inhibition of coronary atherosclerosis by propranolol in behaviorally predisposed monkeys fed an atherogenic diet. *Circulation*. 1987;76:1364–1372.
38. Hedblad B, Wikstrand J, Janzon L, Wedel H, Berglund G. Low-dose metoprolol CR/XL and fluvastatin slow progression of carotid intima-media thickness: main results from the Beta-Blocker Cholesterol-Lowering Asymptomatic Plaque Study (BCAPS). *Circulation*. 2001;103:1721–1726.
39. Wiklund O, Hulthe J, Wikstrand J, Schmidt C, Olofsson SO, Bondjers G. Effect of controlled release/extended release metoprolol on carotid intima-media thickness in patients with hypercholesterolemia: a 3-year randomized study. *Stroke*. 2002;33:572–577.
40. Berger JS, Roncaglioni MC, Avanzini F, Pangrazzi I, Tognoni G, Brown DL. Aspirin for the primary prevention of cardiovascular events in women and men: a sex-specific meta-analysis of randomized controlled trials. *JAMA*. 2006;295:306–313.
41. Ikonomidis I, Andreotti F, Economou E, Stefanadis C, Toutouzas P, Nihoyannopoulos P. Increased proinflammatory cytokines in patients with chronic stable angina and their reduction by aspirin. *Circulation*. 1999;100:793–798.
42. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *N Engl J Med*. 1997;336:973–979.
43. Cyrus T, Yao Y, Tung LX, Pratico D. Stabilization of advanced atherosclerosis in low-density lipoprotein receptor-deficient mice by aspirin. *Atherosclerosis*. 2006;184:8–14.
44. Brown BG, Zhao XQ, Sacco DE, Albers JJ. Lipid lowering and plaque regression. New insights into prevention of plaque disruption and clinical events in coronary disease. *Circulation*. 1993;87:1781–1791.
45. Libby P, Sasiela W. Plaque stabilization: can we turn theory into evidence? *Am J Cardiol*. 2006;98:26P–33P.
46. Brown G, Albers JJ, Fisher LD, et al. Regression of coronary artery disease as a result of intensive lipid-lowering therapy in men with high levels of apolipoprotein B. *N Engl J Med*. 1990;323:1289–1298.