Expression of HMG-CoA reductase in human coronary atherosclerotic plaques and relationship to plaque destabilisation

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Accepted 3 June 2010
Published Online First 19 July 2010

ABSTRACT

Background Little is known about hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase expression in human coronary atherosclerotic plaques.

Objective To investigate the expression of HMG-CoA reductase in coronary atherectomy tissues obtained from patients with unstable and stable angina and examine the relationship of HMG-CoA with plaque instability.

Methods Atherectomy specimens were obtained from 43 patients with unstable (n=22) or stable (n=21) angina who underwent directional coronary atherectomy for de novo coronary artery lesions. The specimens were stained with haematoxylin–eosin and incubated with antibodies specific to HMG-CoA reductase, macrophages, smooth muscle cells and endothelial cells. Histology and immunohistochemistry data were morphometrically evaluated using an image-analysing system.

Results Baseline characteristics were similar between the two groups. Immunopositive areas of HMG-CoA reductase, macrophages, endothelial cells and thrombi were significantly greater in patients with unstable angina than those in patients with stable angina. However, the immunopositive area of smooth muscle cells was not different between the two groups. Macrophage-positive areas correlated well with areas of HMG-CoA reductase in patients with unstable angina ($r=0.72$, $p<0.001$), but not in patients with stable angina ($r=0.02$, $p=0.937$).

Conclusion HMG-CoA reductase was present in coronary atherosclerotic plaques and was more commonly expressed in unstable plaques than in stable plaques. Local HMG-CoA reductase in coronary artery lesions may contribute to plaque instability.

Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase is a rate-limiting enzyme of the mevalonate pathway that produces cholesterol and other isoprenoids.[1] Inhibitors of HMG-CoA reductase (statins) limit cholesterol biosynthesis and also the generation of the isoprenoids involved in inflammatory processes. The benefits of statin therapy in patients with acute coronary syndrome (ACS) appear extremely rapidly.[2–4] The potential mechanisms of these early benefits are not fully understood but are probably not attributable to altered lipid profiles, which require a longer duration of treatment.[1 5–7]

HMG-CoA reductase is a ubiquitous enzyme present in vascular and inflammatory cells, as well as hepatocytes.[1 8] In the vessel wall, HMG-CoA reductase may produce isoprenoids and induce inflammatory responses with plaque destabilisation.[8] Statins are likely to penetrate the vessel wall and rapidly stabilise vulnerable plaques by directly inhibiting the HMG-CoA reductase in lesions.[8 9] Little is known, however, about the expression of HMG-CoA reductase in human coronary atherosclerotic plaques and its relation to ACS.

In this study, we investigated the expression of HMG-CoA reductase in coronary atherectomy tissues retrieved from patients with unstable and stable angina and examined the relationship of HMG-CoA reductase to plaque instability.

METHODS

Study population

A total of 43 native coronary plaques were obtained from 43 patients undergoing directional coronary atherectomy. Clinical and procedural information were prospectively obtained. Patients were classified as having unstable (n=22) or stable angina (n=21) and each specimen corresponded to a single patient's de novo lesion that was responsible for the clinical presentation. Stable angina was defined as typical exertional angina without symptom change within 1 month before the procedure, and unstable angina as acute rest angina (within the previous 48 h, Braunwald class 3B) or subacute rest angina (2–30 days previously, Braunwald class 2B). A culprit lesion was identified based on angiographic lesion morphology, functional studies and intravascular ultrasound findings. The atherectomy procedures of the culprit lesion were carefully performed with intravascular ultrasound guidance. Atherectomy specimens were immediately removed from the cutter housing and immersed in 2-methybutane solution, then stored in a nitrogen tank. The study protocol was approved by the institutional review committee and all patients provided informed consent. Tissue preparation and immunohistochemical staining were carried out using standard methods.[10]

Tissue preparation

Tissue specimens were entirely embedded in OCT compound (Miles, Diagnostics Division, Elkhart, Indiana, USA), snap-frozen in liquid-nitrogen-cooled isopentane (Sigma-Aldrich, St Louis, Missouri, USA) and stored at −70°C until used. The samples were cryosectioned (4 μm thick) onto

superfrost plus microscope slides and were immediately fixed in cold acetone for 10 min and then stored at −70°C for subsequent staining.

Histological analysis

The areas for each plaque were quantified by computer-aided planimetry of each specimen using an acquisition program (Motic Images Advanced 3.2, Motic, China). Plaques were classified as atheroma (ie, necrotic cores and cholesterol clefts without connective tissue matrix) or fibrocellular. Fibrocelluar plaque is further graded into paucicellular (<100 spindled cells in one high-power field) and hypercellular (≥100 spindled cells in one high-power field). Slides were reviewed independently by two pathologists (IH and C-SP) without knowledge of the clinical status.

Immunohistochemistry

The following primary antibodies were used: anti-smooth muscle actin (1A4, DAKO, Carpenteria, California, USA), anti-CD68 (anti-human macrophage antibody clone KP-1, DAKO), anti-CD31 (PECAM-1, Chemicon, Temecula, California, USA) and anti-HMG-CoA reductase (1:250 Polyclonal, Upstate, New York, USA). Immunohistochemistry was carried out using the Envision Plus immunostaining kit (Envision+ Kits, DAKO), according to the manufacturer's instructions. Briefly, primary antibodies (diluted in antibody diluent, DAKO) were applied for 2 h and washed twice with phosphate-buffered saline Tween (PBST) for 5 min each time. Relevant labelled polymer-horseradish peroxidase secondary antibodies (DAKO) were subsequently added for 1 h. As negative controls, adjacent sections were stained with species-matched and isotype-matched irrelevant antibodies, including normal rabbit IgG (Jackson Immunoresearch, Pennsylvania, USA), instead of the primary antibodies. Positive controls were titrated using human breast tissue with apocrine changes for anti-HMG-CoA reductase antibodies. To identify the cell types that stained for HMG-CoA reductase, we also performed immunostaining on serial sections with HMG-CoA reductase and the above antibodies. Immunopositive areas were expressed as ratios of positively stained areas per total tissue area.

Confocal staining

The frozen sections were hydrated in PBS for 10 min at room temperature, incubated with DakoCytomation Protein Block for 5 min at room temperature and then washed three times in PBST. Sections were incubated with mouse anti-human CD68 and rabbit anti-human HMG-CoA reductase monoclonal antibody for 60 min at room temperature. After three additional PBST washes, the sections were incubated with FITC-conjugated anti-mouse IgG and TRITC-conjugated anti-rabbit IgG antibodies for 60 min at room temperature. After three additional PBST washes, the cover slips were mounted on a glass slide using DAKO Fluorescent Mounting Medium (DAKO). Images were collected on a Leica TCS_NT/SP confocal microscope (Leica Microsystems, Mannhein, Germany) using a ×40 objective NA 0.75, zoom ×1–4. Fluorochromes were excited using an argon laser at 488 nm for FITC and a Gre/Ne laser at 543 nm for TRITC. Detector slits were configured to minimise any cross-talk between the channels. Images were processed using the Leica TCS_NT/SP software (version LCS) and Adobe Photoshop 7.0. To visualise cholesterol accumulation in cells, filipin staining (F9765, Sigma-Aldrich) was performed according to the instruction manual.[11] Filipin was excited using a UV filter set (340–380 nm excitation, 40 nm dichroic, 430 nm long-pass filter).

Table 1 Clinical characteristics

Characteristics	Unstable angina (n =22)	Stable angina (n=21)	p Value
Age, years	57.3±9.0	61.5±5.7	0.079
Sex, male/female	19/3	13/8	0.088
Current smoker	6 (27.3)	1 (4.8)	0.095
Diabetes mellitus	7 (31.8)	8 (38.1)	0.755
Hypertension	12 (54.5)	14 (66.7)	0.537
Total cholesterol (mg/dl)	167.8±8	164.9±26.4	0.779
Triglyceride (mg/dl)	143.1±86.6	180.8±134.9	0.283
HDL cholesterol (mg/dl)	40.5±10.4	41.4±11.0	0.798
High sensitivity CRP (mg/dl)	0.97±2.31	0.22±0.25	0.145
Target artery			0.472
Left anterior descending coronary	17 (77.3)	15 (71.4)	
Left circumflex	1 (4.5)		
Right coronary	4 (18.2)	6 (28.6)	
Multivessel disease	11 (50)	7 (33.3)	0.358
Drugs at the time of DCA			
Aspirin	22 (100)	21 (100)	1.0
Clopidogrel	22 (100)	21 (100)	1.0
ACEI	2 (9.1)	2 (9.5)	1.0
β Blockers	10 (45.5)	6 (28.6)	0.347
Calcium antagonists	14 (63.6)	16 (76.2)	0.510
Statins	4 (18.2)	6 (28.6)	0.488

Results are shown as mean±SD or number (%).
ACEI, angiotensin-converting enzyme inhibitor; CRP, C-reactive protein; DCA, directional coronary atherectomy; HDL, high-density lipoprotein.

Statistical analysis

Data were expressed as mean±SD for continuous variables and as frequencies for categorical variables. Continuous variables were compared using the Student t test or the Mann-Whitney U test and categorical variables were analysed using the χ^2 or Fisher's exact test. A linear regression analysis was used to correlate areas stained for HMG-CoA reductase with other variables. Statistical significance was defined as a two-sided p value <0.05.

RESULTS

Clinical characteristics

Baseline characteristics were similar in the two groups (table 1). The mean patient age was 59.4±7.8 years (range 36–71), 74.4% of the patients were men and 34.9% had diabetes mellitus. Of patients with unstable angina, three patients (13.6%) had acute

Table 2 Histological characteristics

Variables	Unstable angina (n=22)		Stable angina (n=21)		p Value*
	mm²	%	mm²	%	
Histology					
Atheroma	112.4±63.4	45.3±21.6	95.3±64.4	49.3±28.0	0.384
Paucicelluar	144.6±135.3	44.0±21.3	95.7±99.5	44.7±26.9	0.932
Hypercellular	21.6±21.4	7.1±5.2	10.6±13.8	5.8±6.9	0.486
Thrombus	6.2±13.5	2.9±6.6	0.1±0.3	0.01±0.05	0.020
Calcium	1.5±3.7	0.6±1.4	0.3±0.7	0.2±0.4	0.219
Total plaque area	286.5±183.4		202.0±128.4		0.087
Immunohistochemistry					
α-SM actin	62.7±64.6	21.4±18.7	63.4±53.3	33.6±28.7	0.103
CD31	5.3±5.5	3.4±4.1	0.6±0.8	0.3±0.5	0.002
CD68	23.9±29.7	10.9±16.2	3.7±4.0	1.8±1.7	0.016
HMG-CoA reductase	6.3±8.6	3.0±4.5	0.7±1.3	0.4±0.7	<0.001

*p-value of the percentage of immunopositive areas between unstable and stable angina.
SM, smooth muscle.

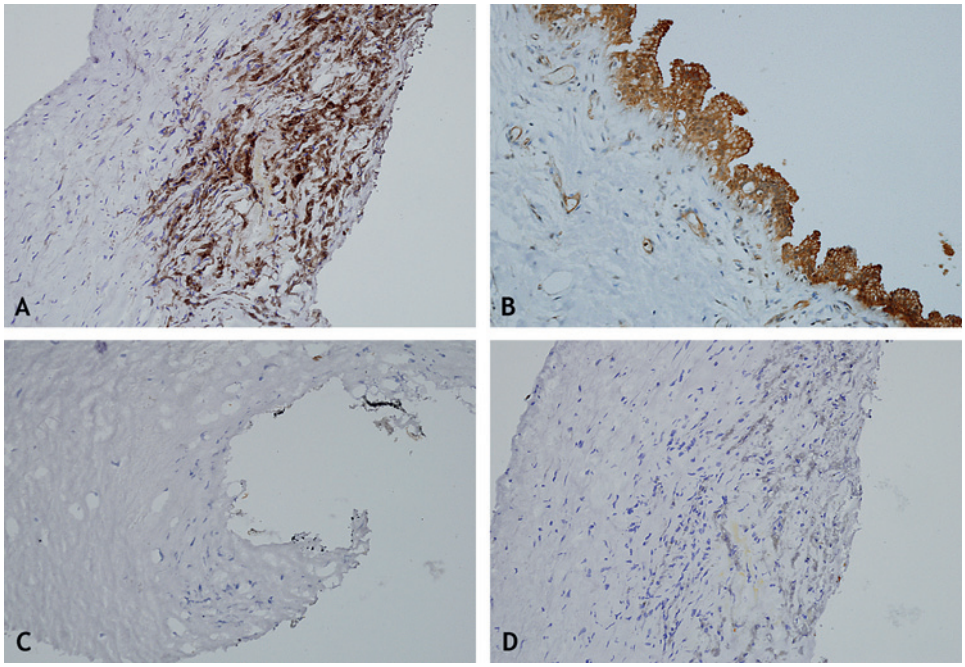

Figure 1 Representative immunohistochemical staining of HMG-CoA reductase. (A) HMG-CoA reductase was strongly expressed on the tissue from a patient with unstable angina (×100, brown). (B) Positive control of breast gland with apocrine change showed immunopositivity for HMG-CoA reductase antibody (×200, brown). (C) Few immunopositive cells were identified on plaque of stable angina. (×100, brown). (D) The coronary plaque in unstable angina without primary antibody of HMG-CoA reductase (negative control) showed no immunoreactivity (×100, brown).

rest angina and 19 patients (86.4%) had subacute rest angina. All patients were taking antiplatelet agents and 10 patients (23.3%) were receiving low-dose statin therapy at the time of directional coronary atherectomy.

Histological analysis

Total plaque areas, atheroma areas and plaque types were similar between the groups (table 2). Calcium was identified in 19.0% of specimens from patients with unstable angina versus 36.4% of

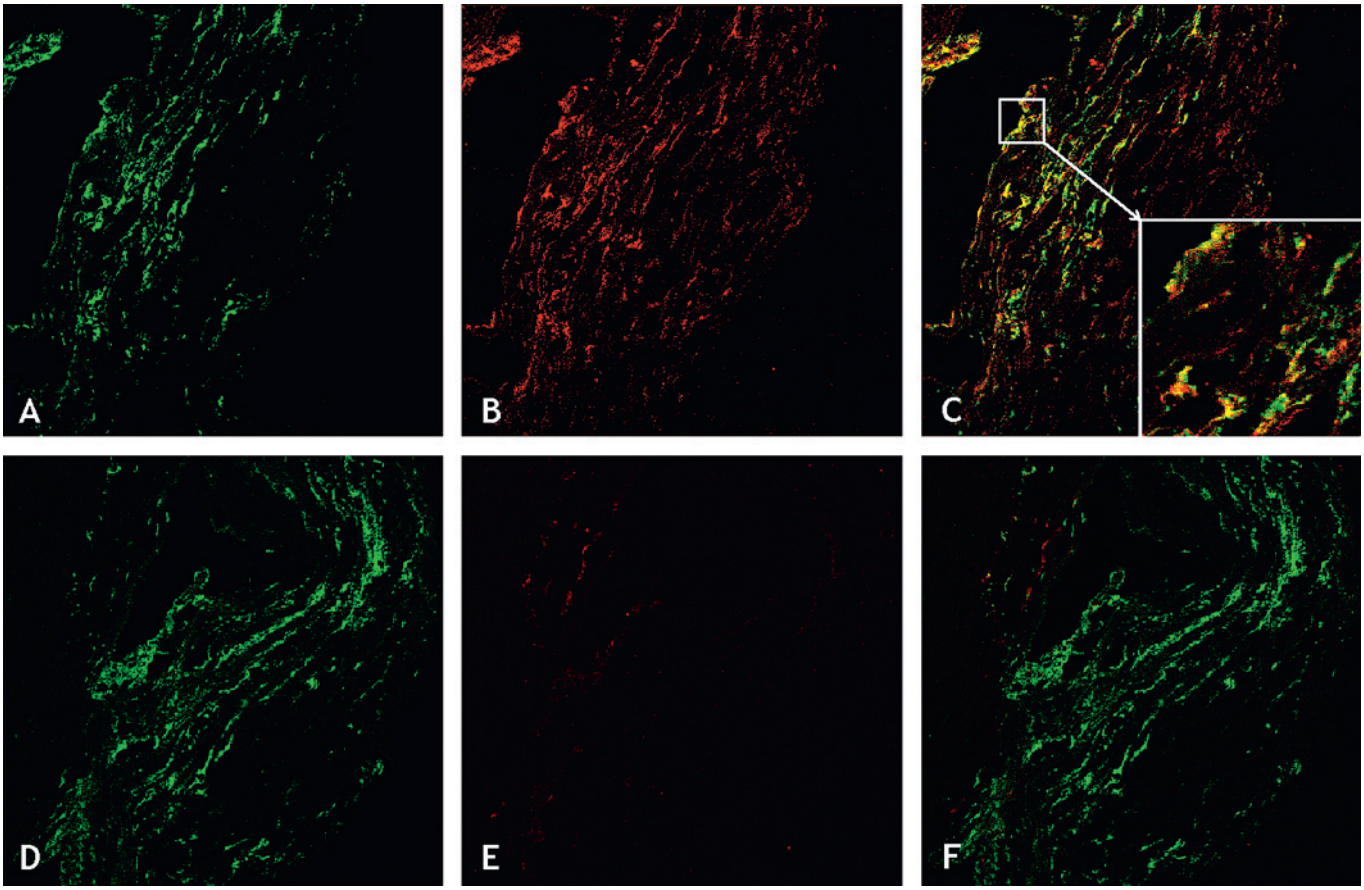

Figure 2 Confocal immunodouble staining of coronary plaque from patients with unstable (A, B, C) and stable angina (D, E, F) (magnification ×400). (A and D) Macrophages were stained with CD68 (FITC-conjugated anti-mouse IgG) antibody (green). (B and E) HMG-CoA reductase was stained with HMG-CoA reductase (TRITC-conjugated anti-rabbit IgG) antibody (red). (C and F) CD68 and HMG-CoA reductase immunostainings were merged, showing colocalisation of both antigens in C (yellow) but not in F. The framed area in C was enlarged (original magnification ×800).

specimens from patients with stable angina (p=0.310). Thrombi were more commonly seen in unstable angina than in stable angina (31.8% vs 4.8%, respectively, p=0.046).

Immunohistochemistry

The immunopositive areas of HMG-CoA reductase (6.3±8.6 vs 0.7±1.3, respectively, p=0.006) and CD68 (23.9±29.7 vs 3.7±4.0, respectively, p=0.005) were significantly larger in patients with unstable angina than in those with stable angina (table 2). The percentage of HMG-CoA reductase immunopositive areas (3.0±4.5 vs 0.4±0.7, respectively, p<0.001) and CD68 immunopositive areas (10.9±16.2 vs 1.8±1.7, respectively, p=0.016) were also significantly greater in patients with unstable angina than in those with stable angina. Likewise, the ratio of HMG-CoA reductase positive area to CD68 positive area was significantly greater in unstable angina than in stable angina (0.98±2.56 vs 0.29±0.59, respectively, p=0.006). Immunopositive areas of endothelial cells and its proportion were greater in unstable angina than in stable angina. However, immunopositive areas of smooth muscle cells and its proportion were not different between the two groups.

Representative immunohistochemical stainings are shown in figure 1, demonstrating a strong immunopositivity with HMG-CoA reductase antibody in unstable angina but weak staining in stable angina. The same areas were stained with CD68 antibody, and double immunostaining by confocal colocalisation confirmed that HMG-CoA reductase immunopositive cells were mainly CD68-positive macrophages (figure 2). Interestingly, CD68 immunopositive cells in unstable angina displayed strong immunoreactivity for HMG-CoA reductase, whereas those in stable angina showed weak immunopositivity. In addition, the filipin staining areas as a marker for cholesterol coincided with the HMG-CoA reductase immunopositive areas (figure 3).

Linear regression analysis showed a significant correlation between the macrophage areas (identified by CD68 immunostaining) and HMG-CoA reductase immunopositive areas (r=0.76, p<0.001). Interestingly, we noted a significant correlation between the two immunopositive areas in patients with unstable angina (r=0.72, p<0.001), but not in patients with stable angina (r=0.02, p=0.937) (figure 4). There was an insignificant weak correlation between HMG-CoA reductase immunopositive area and CD31 immunopositive area (r=0.27, p=0.077). However, no other factors correlated with areas stained for HMG-CoA reductase.

DISCUSSION

This study showed that HMG-CoA reductase was present in human coronary atherosclerotic plaques, that expression levels were greater in unstable plaques and that the immunopositive cells were mostly macrophages. These findings support a potential role for HMG-CoA reductase in the pathogenesis of ACS and may help to explain the early benefits of statin therapy in patients with ACS.

Plaque rupture is a key event in the pathogenesis of ACS and percutaneous coronary intervention may stabilise the culprit lesion. However, many patients still experience recurrent events during the early period after ACS that are characterised by the reflection of multifocal plaque instability throughout the coronary arteries.[12 13] The MIRACL and PROVE-IT trials found that the reduction in clinical events among patients receiving high-dose statin therapy was apparent as early as 30 days after the start of treatment.[2 3] In the ARMYDA-ACS trial, short-term pretreatment with high-dose atorvastatin improved the clinical outcomes of patients with ACS who were undergoing an early invasive strategy, demonstrating the very rapid benefits of statin therapy.[4] These findings conflict with the results of statin trials examining stable patients with coronary artery disease, in which statin therapy showed no apparent benefits by 6–12 months.[5] The early benefits of statin therapy seem to arise from

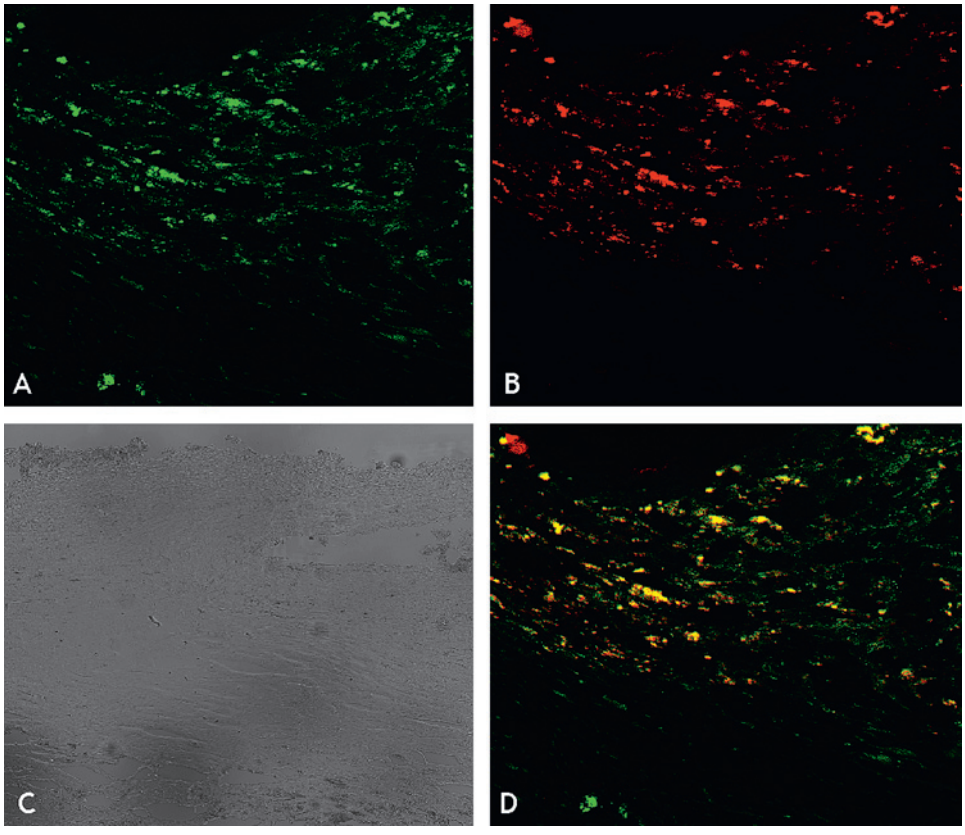

Figure 3 HMG-CoA reductase and filipin staining of coronary plaque from a patient with unstable angina. (A) HMG-CoA reductase (FITC-conjugated anti-rabbit IgG antibody) staining (green). (B) Filipin staining (red). (C) Negative control. (D) Colocalisation of both HMG-CoA reductase and filipin staining (yellow, original magnification ×800).

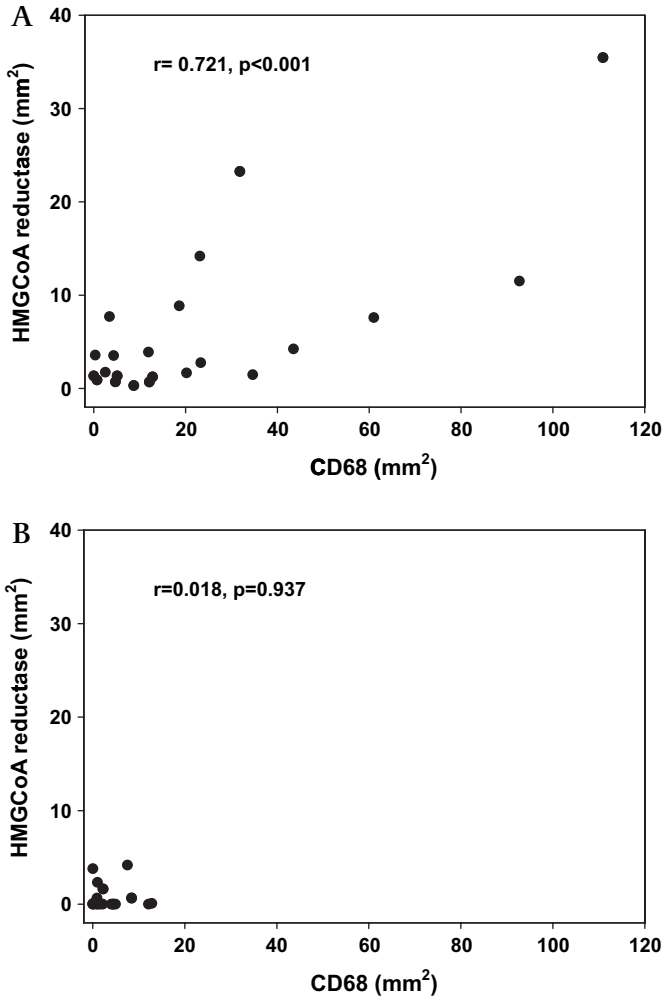

Figure 4 Relationship between CD68-positive areas (mm^2) and HMG-CoA reductase-positive areas (mm^2) in patients with unstable angina (A) or stable angina (B).

cholesterol-independent, pleiotropic effects, but the exact mechanisms remain to be determined.

Inflammation seems to be a pivotal process that transforms stable plaques to unstable plaques, and lesion macrophages have a central role in the pathogenesis of ACS. In addition to their lipid-lowering action, statins can inhibit the synthesis of isoprenoids, which are lipid attachments for a variety of intracellular signalling molecules, such as Rho, Rac and cdc42, thereby mediating the pleiotropic effects.[1] Microarray studies have shown overexpression of HMG-CoA reductase in macrophage-rich areas of human atherosclerotic plaques.[8]

In this study, we showed that HMG-CoA reductase is highly expressed in the unstable plaques of patients with ACS and that macrophages are responsible for the production of HMG-CoA reductase. Local HMG-CoA reductase may promote vascular inflammation by inducing the expression of adhesion molecules and the migration of inflammatory cells.[14 15] Recent studies have shown that high-dose atorvastatin pretreatment before percutaneous coronary intervention reduces periprocedural myocardial infarction, suggesting a rapid plaque stabilising effect of statins.[4] Periprocedural myocardial infarction after stent implantation is related to plaque burden and plaque characteristics.[16 17] Friable plaques in patients with ACS are more likely to be liberated than stable fibrotic plaques. Our results demonstrate the high expression of local HMG-CoA reductase in unstable plaques and the reduced expression of local HMG-CoA in stable plaques. There was also a positive correlation between areas of HMG-CoA reductase expression and macrophage-positive areas. Moreover, filipin staining for the detection of cholesterol accumulation[11] demonstrated that the filipin staining areas coincided with the HMG-CoA reductase staining areas. These findings suggest that local HMG-CoA reductase is functionally active, and lesion macrophages in unstable angina more actively produce HMG-CoA reductase than in stable angina. Statin therapy may rapidly inhibit vascular HMG-CoA reductase and attenuate macrophage function by dampening of plaque inflammation, subsequently decreasing the risk of plaque embolisation after percutaneous coronary intervention to unstable plaque. In contrast, the positive areas for macrophage and HMG-CoA reductase were smaller in stable plaque than in unstable plaque. These findings may account for the potentially different effects of statins according to clinical presentation. Inappropriate induction of HMG-CoA reductase in lesion macrophages may aggravate coronary plaque inflammation, leading to the recurrence of ACS.

In our study, 23.3% of patients were taking low-dose statins before admission. Interestingly, use of statins was not related to HMG-CoA or CD68 immunopositive areas. Recently, the ARMYDA-RECAPTURE study demonstrated that an acute reload of high-dose atorvastatin in patients receiving chronic statin therapy can induce the same cardioprotective effect during percutaneous coronary intervention.[18] The benefit was primarily derived from a reduction in periprocedural myocardial infarction, largely localised to patients who presented with ACS as compared with stable angina. These findings suggest that high-dose statin therapy may be needed to completely inhibit lesion HMG-CoA reductase at the sites of active plaque inflammation. Physical properties determine the ability of statins to cross the cell membrane barrier.[1] The lipophilic statins seem to penetrate the vessel wall more effectively than the hydrophilic statins, eliciting direct local anti-inflammatory effects. However, it remains uncertain which statin has a greater early effect in the acute stage of ACS.

Study limitations

This study had several potential limitations. First, tissues were extracted from the lumen sides of the lesions via directional coronary atherectomy, and the media or adventitia could not be assessed. Furthermore, calcified, tortuous or small vessels are not suitable for directional coronary atherectomy. It remains unclear whether biopsies from these lesions would affect the present results. Finally, owing to the small amount of tissue specimens, immunohistochemistry results could not be confirmed by western blot analysis.

Funding The Korean Society of Interventional Cardiology (2007-1) and the Korea Health 21 R&D Project, Ministry of Health & Welfare, Republic of Korea (A090264).

Competing interests None.

Patient consent Obtained.

Ethics approval This study was conducted with the approval of the Asan Medical Center.

Provenance and peer review Not commissioned; externally peer reviewed.

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Images in cardiology

Cardiac amyloidosis in full glory

A 38-year-old man with an initial incidental finding of hypertension and proteinuria progressed to dyspnoea and hypotension within 4 months. Transthoracic echocardiography showed hypertrophic cardiomyopathy with a pathognomonic granular appearance of the myocardium and left ventricular ejection fraction (LVEF) of 35% (figure 1A). There was multiorgan involvement with cardiac MR and endomyocardial biopsy confirming the diagnosis of cardiac AL amyloidosis (figure 1B) and further investigations revealed renal amyloidosis (figure 1C) and an underlying multiple myeloma (figure 1D). Complete disease remission was obtained after chemotherapy with subsequent heart transplantation.

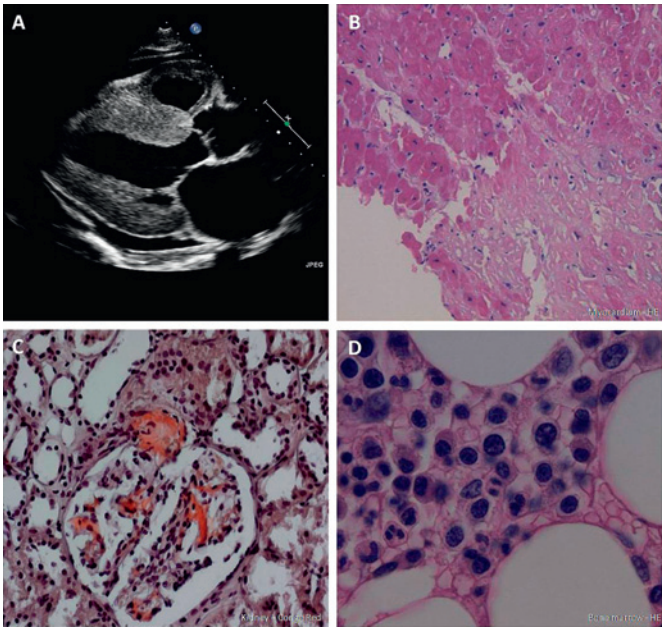

Figure 1 (A) Transthoracic echocardiogram showing hypertrophic cardiomyopathy. (B) H&E stain of endomyocardial biopsy showing amorphous material. (C) Congo Red stain showing deposition of amorphous material in the mesangium and arteriolar blood vessels. (D) H&E stain of bone marrow showing plasma cells and mitotic figures.

Amyloidosis is an uncommon pathogenic process involving the deposition of insoluble proteins as fibrils in organs and tissues resulting in organ failure and death. The most common classification is based on the chemistry of the amyloid fibrils: primary amyloidosis or AL (monoclonal κ or γ chains), secondary amyloidosis or AA (protein A), familial amyloidosis (γ mutant transthyretin), dialysis-associated amyloidosis (β_2-microglobulin) and senile amyloidosis SSA (wild-type transthyretin). Cardiac involvement occurs commonly in primary and familial amyloidosis (congestive heart failure, fatal and non-fatal arrhythmias, hypotension, conduction block and dynamic ventricular outflow tract obstruction). The disease can be rapidly progressive and, in patients with ventricular septum thickness >15 mm, LVEF <40% and symptoms of heart presentation, the median survival may be <6 months.

Cardiac transplantation may be a treatment option in selected subtypes, while chemotherapy and autologous blood stem cell transplantation may increase survival. Early echocardiographic diagnosis is crucial, but assessing the severity of systemic disease to estimate the non-cardiac prognosis remains challenging.

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Competing interests None.

Provenance and peer review Not commissioned; not externally peer reviewed.

Published Online First 24 January 2011

Heart 2011;**97**:720. doi:10.1136/hrt.2010.215707

Heart

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Heart 2011 97: 715-720 originally published online July 19, 2010
doi: 10.1136/hrt.2009.190934