Table 2. Analysis of Events per Patient

Variable	Strategy A	Strategy B	Statistical Analysis
Number of patients with FVT (%)	10 (7.5)	13 (9.8)	OR 1.33 (95% CI 0.56–3.15); p = 0.51
Mean of FVT per patient	0.20 ± 1.01	0.14 ± 0.50	95% CI of the difference: −0.14, 0.25; p = 0.6
Number of patients with HES secondary to FVT (%)	2 (1.5)	12 (9)	OR 0.27 (95% CI 0.07–0.99); p = 0.01†
Mean of HES per patient secondary to FVT	0.02 ± 0.12	0.14 ± 0.54	95% CI of the difference: −0.21, −0.02; p = 0.015
HES/FVT (%)	3/27 (11)	20/22 (91)	OR 0.14 (95% CI 0.04–0.40); p < 0.001
FVT episode duration, s (range)	9.3 ± 8.4 (5–40)	14.8 ± 4.6 (8–29)	95% CI of the difference: −9.96 to −1.07; p = 0.016
Syncope for FVT (%)	2/27 (7.4)*	5/22 (22.7)	OR 0.21 (95% CI 0.04–1.56); p = 0.21†
Near-syncope for FVT (%)	1/27 (3.7)	12/22 (54)	OR 0.10 (95% CI 0.01–0.07); p < 0.001†
Syncope/near-syncope for FVT (%)	3/27 (11)	17/22 (77)	OR 0.18 (95% CI 0.06–0.52); p < 0.001
Mean CL	288 ± 15	284 ± 16	0.48

*The two episodes of syncope in strategy A occurred secondary to fast VT unsuccessfully treated by ATP. †Fisher exact test.
CI = confidence interval; CL = cycle length; FVT = fast ventricular tachycardia; HES = high-energy shocks; OR = odds ratio.

in the FVT zone and may improve the clinical tolerance of these tachycardias.

In re-entrant VT, the ability of ATP to terminate the arrhythmia depends on the presence of an excitable gap (6) and on the capability of the impulses to penetrate this gap. The main limiting factor for penetrating the excitable gap is the distance to the circuit; therefore, a long burst or a short-pacing CL is needed to reach the FVT circuits. The first burst that we selected was shorter and faster than those previously reported; nevertheless, the efficacy and acceleration rate were similar, suggesting that the shorter CL might compensate for a lower number of beats in the initial ATP train (1). This observation may be important to decrease the delay before the rescue HES is delivered if needed.

The number of FVTs is lower than in previous studies; however, the proportion of patients with FVT is similar. The high proportion of patients treated with beta-blockers and the inclusion of nonischemic patients may explain this difference. The use of ATP also appears to reduce the incidence of syncope/near-syncope associated with an episode of FVT, presumably as a result of a reduction in the VT duration. Interestingly, beta-blockers increased the efficacy of ATP, indicating a possible influence of autonomic tone in the maintenance of the VT (7,8).

This study suggests that a single, short ATP burst is efficient and safe for the treatment of FVT, reducing the HES incidence and arrhythmia-related symptoms. Nevertheless, the small number of episodes and patients limits the power of these conclusions and, therefore, a larger prospective study is required to validate these data.

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Simvastatin Improves Endothelial Function in Patients With Rheumatoid Arthritis

To the Editor: Rheumatoid arthritis (RA) is the most common systemic connective tissue disease and affects 2.1 million people in the U.S., 1.5 million of whom are women (1). Patients with RA are at increased risk of developing premature cardiovascular disease, which shortens life expectancy by 3 to 18 years (1). These data provide the rationale for preventive measures at an early stage before overt cardiovascular disease becomes evident. Interestingly, endothelial dysfunction, the key event in early atherogenesis, just recently has been described in patients with RA both with high and low disease activity (2).

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Table 1. Baseline Characteristics

	Baseline (n = 20)
Age (yrs)	57 ± 2
Women	14 (70)
Positive rheumatoid factor	15 (75)
Erosive disease	14 (70)
Disease duration (yrs)	14 ± 2
Cardiovascular risk factors	
Smoking in the past (%)	5 (25)
Arterial hypertension (%)	8 (40)
Diabetes mellitus (%)	0
Positive family history (%)	2 (10)
Body mass index (kg/m^2)	23.8 ± 0.6
Cardiac medication (%)	
Low-dose aspirin	3 (15)
Beta-blockers	3 (15)
Angiotensin converting enzyme inhibitors/ angiotensin II receptor blockers	4 (20)
Antirheumatic therapy	
Disease-modifying antirheumatic drugs	17 (85)
Methotrexate	13 (65)
Other disease-modifying antirheumatic drugs	4 (20)
Prednisone	11 (55)
Nonsteroidal anti-inflammatory drugs	17 (85)

Results expressed as mean ± SEM, or n (%).

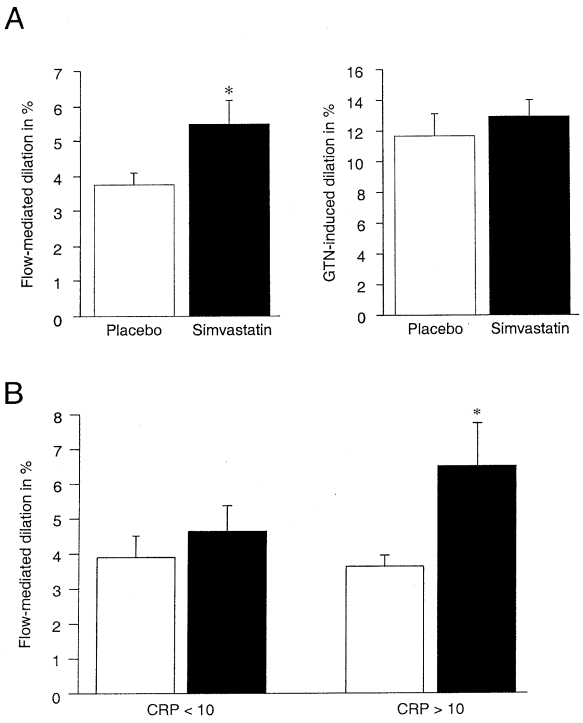

Figure 1. (A) Flow-mediated dilation was increased after four weeks of simvastatin therapy (p = 0.02 vs. placebo). Endothelium-independent function assessed by glycerol trinitrate (GTN)-induced vasodilation remained unchanged (p = 0.58 vs. placebo). **(B)** Flow-mediated dilation in 10 patients with high and in 10 patients with low inflammation markers. Patients with elevated markers of systemic inflammation (n = 10; C-reactive protein [CRP] >10 mg/l) showed pronounced improvement in flow-mediated dilation (vs. patients with CRP <10 mg/l, n = 10; p = 0.04). **Open bars** = placebo; **closed bars** = simvastatin.

Statins have demonstrated beneficial effects in primary and secondary prevention trials in a wide range of cardiovascular risk categories (3). In addition to their potent lipid-lowering effects, statins recently have been ascribed anti-inflammatory, antithrombotic, antioxidative, and immunomodulatory properties (4,5). Hence, the aim of the present study was to evaluate the effects of statin therapy on vascular function, plasma lipids, and oxidative stress in patients with RA who have normal cholesterol levels.

The present study was a randomized, crossover, double-blind and placebo-controlled interventional trial. Twenty patients were assigned randomly to receive either simvastatin 40 mg/day for four weeks followed by four weeks of matching placebo or vice versa. Endothelial function and laboratory and clinical parameters were assessed at baseline and the end of each treatment phase as described previously (2). Inclusion criteria were diagnosis of RA according to the revised American College of Rheumatology diagnostic criteria (6), age 18 to 65 years, and active disease, defined as Disease Activity Score in 28 joints of >2.6 (Table 1). Exclusion criteria were previous myocardial infarction, coronary intervention or coronary surgery, previous treatment with statins in the last six months, uncontrolled hypertension (>160/90 mm Hg), dyslipidemia (low-density lipoprotein [LDL] cholesterol >4.9 mmol), smoking, and kidney (creatinine >150 μmol/l) or liver disease. Disease-modifying antirheumatic drug therapy was unchanged for three months before inclusion to the study and remained stable throughout. Of the 20 patients studied, 13 received methotrexate, with an average dose of 16 mg/week, that was administered subcutaneously once a week. Concomitant medication, including corticosteroids (average oral dose of 3.4 mg/day) or nonsteroidal anti-inflammatory drugs and folic acid (average dose 7 mg/week), remained unchanged throughout the study course. Each patient gave written informed consent before entry into the study. The study protocol was approved by the local ethics committee of the University Hospital of Zürich.

This study is the first to show that statin therapy reduces plasma cholesterol and oxidative stress in the context of ongoing inflammation, thus resulting in an improvement of vascular function in normocholesterolemic patients with RA. Flow-mediated dilatation as a measurement of endothelial function improved after four weeks of treatment with simvastatin compared with placebo (5.5 ± 0.7% vs. 3.8 ± 0.4%; p = 0.02) (Fig. 1A). Stratified by median split, patients with higher markers of inflammation (n = 10; C-reactive protein >10 mg/l) showed a significantly higher improvement in flow-mediated dilation than patients with low markers of inflammation (n = 10; C-reactive protein <10 mg/l; p = 0.04) (Fig. 1B). There was no difference concerning the treatment sequence. Total cholesterol, LDL cholesterol, and apolipoprotein B (apoB) were lowered by simvastatin therapy by 21%, 34%, and 33%, respectively (p < 0.0001) (Table 2). Oxidized low-density lipoproteins (oxLDLs), as well as the ratio oxLDL to LDL (p < 0.001 and p = 0.03, respectively), were reduced by simvastatin treatment (Table 2), indicating attenuated oxidative stress.

Although modest but clinically apparent anti-inflammatory effects of atorvastatin were reported just recently by McCarey et al. (7), the effects of statins on vascular function in systemic connective tissue disease, particularly in patients with RA who had low serum cholesterol levels without overt cardiovascular disease, were unclear before this study. The improvement of endothelial function in the present study may be explained partly by the reduction of LDL cholesterol and apoB. The sum of apoB concentrations in all atherogenic particles provides better risk prediction than LDL

Table 2. Clinical Parameters, Laboratory Values, and Vascular Function at the End of the Study

	Simvastatin (n = 20)	Placebo (n = 20)	p Value
Vital signs			
Blood pressure, mm Hg	126/77 ± 4/2	131/82 ± 5/2	0.83/0.07
Mean blood pressure, mm Hg	93.3 ± 2.7	98.1 ± 3.1	0.21
Heart rate, beats/min	66 ± 2	69 ± 2	0.37
Laboratory			
Total cholesterol, mmol/l	4.1 ± 0.3	5.2 ± 0.3	<0.0001
LDL cholesterol, mmol/l	2.0 ± 0.2	3.0 ± 0.2	<0.0001
Oxidized LDL, U/l	42.6 ± 4.5	63.0 ± 4.9	<0.0001
Oxidized LDL/LDL ratio	23.3 ± 2.2	32.3 ± 2.8	0.03
HDL cholesterol, mmol/l	1.5 ± 0.1	1.5 ± 0.1	0.39
Triglycerides, mmol/l	1.3 ± 0.2	1.6 ± 0.2	0.06
Apolipoprotein B, g/l	0.7 ± 0.1	1.1 ± 0.1	<0.0001
Lipoprotein(a), mg/l	162 ± 55	165 ± 55	0.60
C-reactive protein, mg/l	20.9 ± 7.5	22.9 ± 8.8	0.58
Erythrocyte sedimentation rate, mm/h	23.1 ± 5.1	23.0 ± 4.9	0.96
Interleukin-1, pg/ml	0.1 ± 0.1	0.2 ± 0.1	0.77
Interleukin-6, pg/ml	9.2 ± 2.2	8.5 ± 2.0	0.83
Tumor necrosis factor-alpha, pg/ml	10.3 ± 7.7	9.2 ± 7.0	0.16
Glucose, mmol/l	5.1 ± 0.3	5.0 ± 0.2	0.69
Creatinine, μmol/l	78.2 ± 2.9	77.3 ± 2.7	0.42
Creatine kinase, U/l	76.5 ± 8.0	74.7 ± 9.4	0.99
ASAT, U/I	24.2 ± 2.3	20.8 ± 1.3	0.03
ALAT, U/l	26.6 ± 4.2	20.3 ± 1.6	0.11
Vascular function measurements			
Arterial diameter, mm	4.3 ± 0.16	4.4 ± 0.16	0.62
Flow-mediated vasodilation, %	5.5 ± 0.7	3.8 ± 0.4	0.02
Nitrogylcerin-induced vasodilation, %	12.8 ± 1.2	11.7 ± 1.5	0.58
Brachial artery intima media thickness	0.4 ± 0.10	0.4 ± 0.05	0.17
Disease activity score (DAS28)	3.9 ± 0.3	3.7 ± 0.3	0.38
RADAI	2.2 ± 0.4	2.4 ± 0.5	0.21

Results expressed as mean ± SEM.

ALAT = alanine aminotransferase; ASAT = aspartate aminotransferase; HDL = high-density lipoprotein; LDL = low-density lipoprotein; RADAI = Rheumatoid Arthritis Disease Activity Index.

cholesterol alone, particularly in individuals with normal and low LDL cholesterol concentrations (8).

Inflammation is a hallmark both of atherosclerosis and RA (4,9), and striking similarities exist between the pathogenesis of atherosclerotic vascular disease and RA (9). Thus, mechanisms that are responsible for synovial inflammation and subsequent joint destruction may not only be confined to the joints but also evident in the vessel wall, explaining the excess of cardiovascular disease in RA. Interestingly, the improvement of endothelial function in the present study was more pronounced in patients with elevated markers of inflammation, thus extending findings of a recent study demonstrating modest but clinically apparent anti-inflammatory effects of atorvastatin in patients with RA (7).

Endothelial dysfunction is characterized by impaired bioavailability of nitric oxide due to decreased production or accelerated degradation of nitric oxide by reactive oxygen species (10). Indeed, in the present study, simvastatin reduced formation of reactive oxygen species, as indicated by a reduction of oxLDL. Importantly, the reduction of the oxLDL/LDL ratio exceeded that of LDL alone, clearly indicating attenuation of oxidative stress. Oxidized LDL is not only an index of lipid peroxidation, but it also causes endothelial dysfunction itself through the impairment of signal transduction from endothelial cell surface receptors, inhibition of nitric oxide synthase activity, and inactivation of nitric oxide released from endothelial cells (10).

In conclusion, the reduction of proatherogenic lipids and markers of oxidative stress result in an improvement of vascular function, indicating that statins may hold the potential as a novel add-on therapy in the treatment of RA. Yet, the potential hepatotoxicity of statins, especially in combination with other disease-modifying antirheumatic drug therapies, is of clinical concern and needs to be addressed in future clinical studies. The definitive answer as to the net effect of statins on cardiovascular events in patients with RA, can only be provided by well-designed, large-scale clinical trials.

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Impact of Microvascular Complications on Outcome After Coronary Stent Implantations in Patients With Diabetes

To the Editor: Bare metal stent implantation is less effective in patients with diabetes than in patients without diabetes (1–3). Microvascular complications have been identified as risk markers for cardiovascular events in patients with diabetes (4–7). We evaluated the impact of microvascular complications (nephropathy and retinopathy) on the outcome after elective coronary bare metal stent implantation in patients with type 2 diabetes.

A total of 283 consecutive patients with type 2 diabetes mellitus who successfully underwent their first elective bare metal stent implantation at our institution from January 2000 to June 2003 were included into the analysis. Diabetic retinopathy was detected within one week before or after the procedure. Microalbuminuria (protein excretion of 30 to 300 mg/24 h) was determined the day before the procedure.

The principal characteristics of the 283 patients are summarized in Table 1. At 12 months, major adverse cardiac events (major adverse clinical event [MACE], i.e., death of any cause, nonfatal myocardial infarction, repeat percutaneous procedure, and bypass surgery) occurred in 34 of the 161 patients (21%) in the group without microvascular complications, in 18 of the 45 patients (40%) in the nephropathy group, in 22 of the 43 patients (51%) in the retinopathy group, and in 25 of the 34 patients (73.5%) in the group with both microvascular complications ($p < 0.001$) (Fig. 1). The influence of clinical, angiographic, and procedural variables on

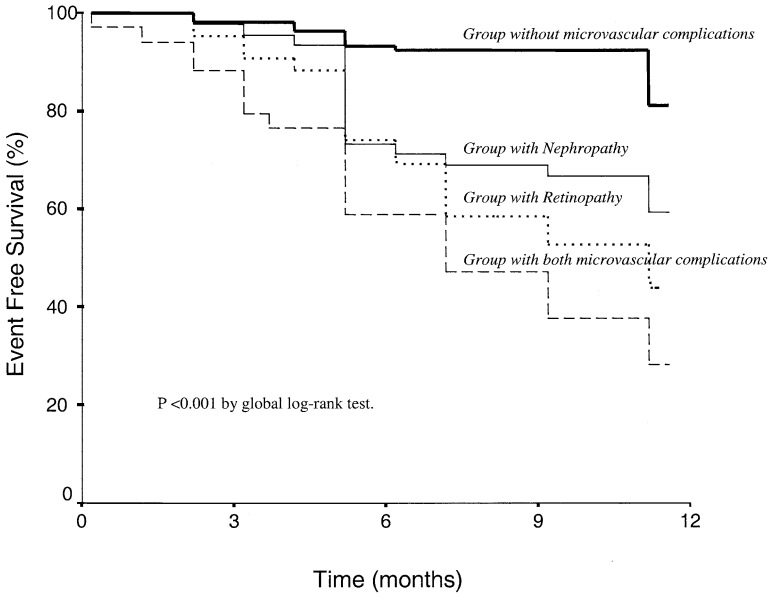

Figure 1. Kaplan-Meier event-free survival at 12 months in four groups defined according to the presence of microvascular complications.