

Effects of lifestyle modification on the progression of coronary atherosclerosis, autonomic function, and angina—The role of GNB3 C825T polymorphism

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Background Given the multimodal medical and interventional treatment options in coronary artery disease, the additional value of intensified lifestyle modification is unclear. We have therefore examined the effects of lifestyle modification on top of current treatment and also associated with the GNB3 C825T polymorphism, which has established association to sympathetic activation and the precipitation of angina.

Methods One hundred one patients with established coronary artery disease were randomized to a 1-year lifestyle modification group (lifestyle group [LG]) or an advice group. Risk factors, coronary calcification (electron beam tomography), heart rate variability, baroreflex sensitivity, anginal symptoms, and quality of life (QOL) were assessed on entry and after 1 year.

Results Patients in LG had excellent program adherence, but lifestyle modification had no impact on metabolic risk factors and coronary calcification. Changes in heart rate, heart rate variability, and blood pressure were only slightly favoring LG. Baroreflex sensitivity increased by 2 (0.79-3.13) ms/mm Hg in the LG but decreased by -0.10 (-1.11 to 0.92) in the advice group ($P = .013$). Lifestyle modification led to improved physical QOL, reductions of anginal attacks (-54% vs 11%, $P = .01$), and dose reductions in 30% of anti-ischemic medications ($P = .004$). *825T allele carriers had a more pronounced reduction of heart rate and improvement of angina and QOL. The beneficial effect on reduction of medication was seen in *825T allele carriers only.

Conclusions In the presence of modern treatments, comprehensive lifestyle modification provides no additional benefits on progression of atherosclerosis but improves autonomic function, angina, and QOL with concomitant reduced need of medication. These responses are more pronounced in GNB3*825T allele carriers. (Am Heart J 2006;151:870-7.)

Comprehensive multifactorial lifestyle modification has achieved beneficial cardiovascular effects in patients with coronary artery disease (CAD) in earlier trials. In 3 randomized trials, patients who adhered to a program of comprehensive lifestyle changes for 1 to 4 years improved symptomatically, and angiography revealed a

modest regression of coronary artery stenoses.¹⁻³ However, the clinical impact of intensified lifestyle modification on top of current medical care in patients with CAD is unknown because all available data from randomized trials were collected before the era of statin therapy and improved coronary interventions. Recent studies on less intense cardiac rehabilitation programs indicate that, after completion of such programs, lifestyle and risk factors do not improve or even deteriorate.^{4,5}

Whether responses to lifestyle modification are individually different and possibly depend on lifestyle-gene interactions is unclear. A C825T polymorphism in the gene GNB3 encoding for the β_3 subunit of heterotrimeric G proteins is associated with alternative splicing and enhanced signal transduction.⁶ The *825T allele is associated with a higher risk for hypertension and obesity.^{6,7} Moreover, *825T allele carriers have enhanced coronary vasoconstriction to sympathetic activation.⁸ Finally, the *825T allele is associated with

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altered cardiovascular drug responses.⁹⁻¹¹ To address the interaction of lifestyle modification with this specific polymorphism, we conducted the randomized controlled SAFE-LIFE trial with a preplanned subgroup analysis of the C825T polymorphism and evaluated the effects on risk factors, coronary calcium, autonomic function, anginal symptoms, quality of life (QOL), and the need of medication. We hypothesized that the lifestyle intervention would result in beneficial changes of the combined primary end points of supine systolic blood pressure (S-SBP), heart rate, heart rate variability (HRV), and psychological QOL after 1 year, and of the Agatston¹² coronary calcium score after 3 years. We here report the 1-year study results.

Methods

Patients with documented CAD were recruited at 2 hospitals after undergoing coronary angiography, percutaneous coronary intervention (PCI), or in-hospital treatment of CAD. Individuals were excluded for any one of the following diagnoses: acute coronary syndrome, coronary artery bypass graft (CABG) within the previous 3 months, type 1 diabetes mellitus, arrhythmias, heart failure, life-threatening comorbidity, or a body mass index (BMI) of >33 kg/m² (a BMI of >33 kg/m² may reduce the quality of electron beam tomography [EBT] measurements).

Study design and randomization

The study was designed as a 1-year randomized controlled trial to be followed up with the pending EBT measurements after 3 years. The protocol of this study was approved by the Ethics Committee of the Medical Faculty of the University of Essen. Written informed consent was obtained from all patients.

Randomized assignments were made centrally by a computer program. Assignments were stratified by age, sex, and status of revascularization. Eligible participants were assigned either to (1) a comprehensive lifestyle modification group with an intensive 100-hour per 1-year program and the nutritional focus on Mediterranean diet (lifestyle group [LG] $n = 48$) or (2) to an advice group (AG $n = 53$) that received printed lifestyle advice only.

Assessment methods

Severity of angina and frequency of angina attacks were assessed with 6-point Likert scales. Quality of life was estimated from the sum scores of the 36-Item Short-Form Health Survey¹³; general perceived change of QOL was assessed on a 5-point Likert scale at follow-up. Patients were inquired about cardiac events, and physician's and hospital records were used to confirm patient-derived information.

Blood pressure, heart rate, HRV, and baroreflex sensitivity

Measurements were done after an overnight fast on medication. After a 5-minute adaptation phase, the protocol included a 30-minute supine deep resting period followed by metronomic breathing (at 9, 12, and 15 cpm). High-frequency

heart rate variability (HF-HRV) and spectral analysis of baroreflex sensitivity (BRS) were calculated from the different paced breathing conditions, as previously described.¹⁴ Baseline heart rate was calculated from the mean of the supine electrocardiogram recordings at deep rest. Arm blood pressure was recorded when patients were seated, followed by 5 recordings supine, with an automatic sphygmomanometer (Dynamap; Criticon, Norderstedt, Germany). Supine systolic blood pressure was derived from the mean of the third and fourth measurement at deep rest. Finger blood pressure (Finapres; Ohmeda, Englewood, CO) was monitored to obtain continuous systolic blood pressure recordings for estimation of BRS. Identical procedures were used for BRS and HF-HRV calculation; ectopic intervals were interpolated for analyses. The defined fixed bandwidths of fast Fourier transformation were 0.070 to 0.1299 Hz (low frequency) and 0.130 to 0.50 Hz (high frequency). All physiological data were analyzed blinded to group assignment.

Electron beam computed tomography

All scans were performed with a C-150 XP/HR EBT scanner (Imatron, San Francisco, CA) according to a standard protocol using the scanner's high-resolution, single-slice mode with 3-mm slice thickness and an acquisition time of 100 milliseconds per image. A single experienced investigator evaluated all EBT scans in a blinded fashion. Coronary artery calcification was determined by the method of Agatston et al.¹² Segments with implanted stents were excluded; if a participant received a new stent during the study, the baseline score was corrected retrospectively with exclusion of the newly stented segment.

Laboratory and genotyping

Blood samples were drawn from participants after overnight fasting and intake of regular medications. Serum lipids were assessed using standard methods. Plasma fatty acids were measured by gas-liquid chromatography. Genotyping was performed as previously described.⁶

Comprehensive lifestyle program and control therapy

The intervention lasted 12 months with decreasing intensity. The program began with a 3-day nonresidential retreat followed by weekly 3-hour meetings for 10 weeks. Thereafter, 2-hour meetings took place every other week for 9 months. The lifestyle program addressed diet, stress management, and physical activity. Lifestyle group participants were extensively informed about the Mediterranean diet by individual nutritional advice, group discussions, and cooking classes. Regular exercise and increased daily activities were strongly recommended but not actively practiced within the group sessions. The stress management was adopted according to a validated program.¹⁵ Patients practiced various relaxation techniques according to personal choice, including meditation, guided imagery, and yoga as well as techniques reducing cognitive and affective components of stress. Participants were asked to practice these techniques at least 30 minutes daily.

Patients in AG received short written lifestyle informations that were mailed shortly after randomization.

Assessment of adherence

Dietary adherence, defined as (1) the exclusive use of olive oil/tapeseed oil, (2) 2 portions of fatty fish per week, and (3)

5 portions of fruits and/or vegetables daily, was assessed with Likert scales and was cross-checked with a validated prospective 7-day food record. Calculation of energy expenditure by exercise was based on a standardized 4-week physical activity questionnaire. Relaxation practice was assessed from self-report. A summarized adherence score was calculated, with 100% adherence defined as 30-minute daily relaxation training, full adherence to dietary key nutrients, and >6276 kJ (1500 kcal) energy expenditure per week during exercise. Patients who did more relaxation and/or exercise than recommended achieved proportional scores > 100%.

Statistical analysis

We compared the effects of lifestyle modification versus advice on change in metabolic variables, Agatston score,¹² heart rate, HF-HRV, BRS, blood pressure, anginal symptoms, intensity of medication, and QOL from baseline to the 1-year follow-up. For between-group comparisons of normally distributed variables (eg, heart rate, BRS, blood pressure, QOL), we used *t* test statistics. The Mann-Whitney *U* test was used for comparison of Agatston scores,¹² HF-HRV, anginal symptoms, and ordinal scales. Difference in proportions (medication) was evaluated using χ^2 test or Fisher exact test, as appropriate. A *P* value of <.05 was considered as statistically significant. The study hypothesis of between-group difference of change in heart rate, HF-HRV, S-SBP, and psychological QOL was tested 2-sided, with adjustment for multiple testing according to Bonferroni-Holm. A linear regression model combined with backward variable elimination was calculated for change in heart rate, with study group, age, sex, revascularization status, baseline heart rate, β -blocker use, prior infarction, and genotype as potential regressors. All statistical computations were performed with SAS v8.2 statistical software (Heidelberg, Germany).

Because the phenotype associated with TT and TC genotype is similar and because of the low number of individuals with TT genotype in white populations,⁶ we combined *825T allele carriers (TT + TC) and compared them with the homozygous GNB3*825C/*825C genotype for the genetic analysis.

Results

Of 235 screened individuals, 105 fulfilled the study criteria and underwent randomization. Of these, 3 patients withdrew from the study (LG 2, AG 1); in addition, 1 LG patient dropped out because of severe comorbidity. Results are presented for the 101 patients who completed follow-up. There were no differences in baseline characteristics between groups (Table I). During the study period, no deaths occurred. Two patients in AG received PCI, 2 patients in LG underwent CABG because of symptom progression. Three further AG patients were hospitalized because of angina, 2 of them with diagnosis of acute coronary syndrome.

Adherence to the program participation in LG was excellent, with only 3 patients attending <90% of all group sessions. Both groups reported improving their diets; significant group differences in favor of LG were

Table I. Baseline characteristics

Characteristics	LG	AG	P
Subjects (n)	48	53	
Age (y)	59 ± 9	60 ± 9	.65
Male-female (n)	38:10	40:13	.66
BMI (kg/m ²)	26.1 ± 3.2	27 ± 2.8	.06
Seated SBP (mm Hg)	145 ± 19	145 ± 18	.95
Seated DBP (mm Hg)	85 ± 13	83 ± 12	.51
Current smoker (%)	16.7	7.5	.15
History of MI (%)	45.8	54.7	.37
Years since last MI	4.8 ± 4.5	6.1 ± 4.7	.91
Coronary bypass (%)	33.3	30.1	.73
PCI (%)	56.2	52.8	.73
Implanted stent (%)	43.7	39.6	.68
Coronary vessels >50% stenosis (%)			
1	31.2	33.9	.77
2	27.1	26.4	.94
3	41.7	39.6	.43
Medication (%)			
Statins	85.4	79.2	.42
Aspirin, Coumadin	97.9	98.1	.94
β -Blockers	75.0	77.3	.79
ACE inhibitors	50.0	49.1	.88
GNB3*825T allele carriers (n)	21	228	.32
GNB3*825C/*825C carriers (n)	27	24	.67

Values are mean \pm SD if not indicated otherwise. SBP, Systolic blood pressure; DBP, diastolic blood pressure; MI, myocardial infarction; ACE, angiotensin-converting enzyme.

related to key features of the Mediterranean diet, that is, increased intakes of ω -3 fatty acids, fruits/vegetables, and olive oil, and decreased intake of saturated fat (each *P* < .01). At baseline, stress reduction training was not practiced in either group. After 1 year, LG patients reported spending 39 \pm 5 minutes daily in relaxation practice versus 5 \pm 8 minutes for AG patients (*P* < .001). Energy expenditure during exercise increased from a mean of 3556.4 to 5313.68 kJ/wk (850 to 1270 kcal/week) in LG but decreased from 4171.448 to 3849.28 kJ/wk (997 to 920 kcal/week) in AG (*P* < .01). The summarized adherence score was 97% (nutrition 75%, relaxation 131%, exercise 84%) in LG patients and 46% (nutrition 63%, relaxation 14%, exercise 61%) in AG patients (*P* < .001). The number of smokers decreased slightly from 8 to 6 in LG and from 4 to 3 in AG.

Metabolic variables and coronary calcium

No significant changes of serum cholesterol and triglycerides levels, and BMI were observed in either group at follow-up. Plasma levels of long-chain ω -3 polyunsaturated fatty acids (PUFAs) increased significantly in LG compared with AG. Patients of LG had nonsignificant reductions in supine blood pressure and modest reductions in heart rate compared with AG (*P* = .005) (Table II).

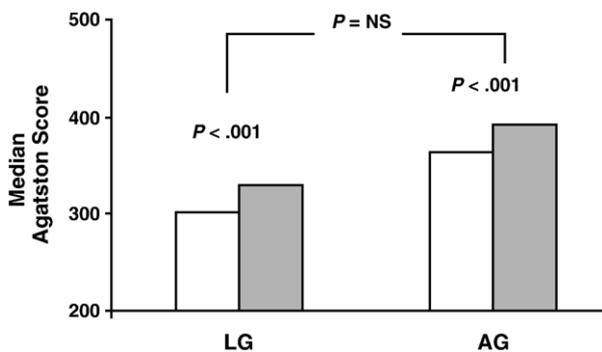
No effect of the lifestyle modification program on coronary calcification was observed. The median annual increase of the Agatston coronary calcium score¹² was

Table II. Metabolic parameters, heart rate, and blood pressure

Variable	LG		AG		P
	Baseline	1 y	Baseline	1 y	
BMI (kg/m ²)	26.1 ± 3.2	25.9 ± 3.0	27 ± 2.8	26.8 ± 2.9	.96
Total cholesterol (mmol/L)	4.8 ± 1.2	4.9 ± 1.1	5.0 ± 1.0	4.8 ± 0.9	.16
LDL-C (mmol/L)	3.2 ± 1.0	3.1 ± 1.1	3.3 ± 0.8	3.0 ± 0.7	.41
HDL-C (mmol/L)	1.4 ± 0.3	1.5 ± 0.4	1.4 ± 0.3	1.4 ± 0.3	.63
Triglycerides (mmol/L)	1.3 ± 0.8	1.3 ± 0.8	1.4 ± 0.8	1.4 ± 0.8	.62
ALA (mg/L)	18.7 ± 8.6	24.1 ± 12.1	22.2 ± 9.9	25.4 ± 10.6	.34
Docosahexaenoic acid (mg/L)	90.9 ± 37.2	107.3 ± 61.4	92.5 ± 47.3	89.1 ± 34.1	.026
Heart rate (beat/min)	61.5 ± 10.4	59.8 ± 8.4	59.2 ± 7.4	61.6 ± 8.8	.005
S-SBP (mm Hg)	129.4 ± 17.6	125.4 ± 13.8	129.5 ± 13.8	128.3 ± 14.1	.27
Supine DBP (mm Hg)	76.7 ± 11.6	74.8 ± 9.9	75.5 ± 9.6	75.3 ± 8.7	.34

Values are mean ± SD. HDL-C, High-density lipoprotein cholesterol.
*P values for between-group difference of change, unadjusted.

Figure 1



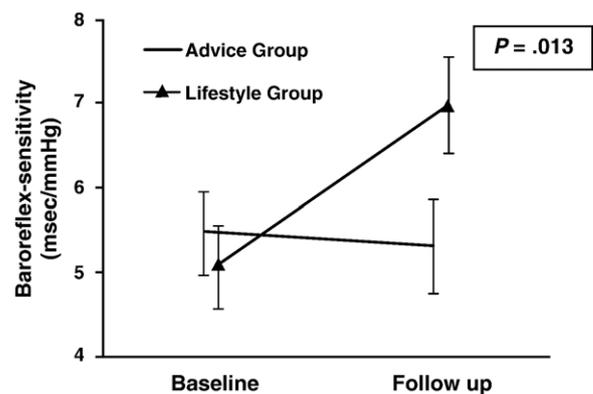
Median Agatston score¹² at baseline (white bars) and follow-up (dark bars) in LG and AG. NS, Not significant.

35 (95% CI 20-61) in LG and 41 (13-66) in AG, representing moderate relative increases of 14.9% versus 16.3% in the 2 study groups (Figure 1). Subanalyses for patients without previous PCI or CABG showed no group differences.

Autonomic function, angina, and QOL

Participation in LG was associated with improved autonomic function. Baroreflex sensitivity increased markedly by 2 (0.79-3.13) ms/mm Hg in LG but decreased by -0.10 (-1.11 to 0.92) in AG (P = .013) (Figure 2). Median HF-HRV slightly increased from 4.9 to 5.1 ms² in LG and decreased from 5.1 to 5.0 in AG (P = .03). The improvement of autonomic function was paralleled by a decrease in angina pectoris severity and an increase in physical QOL. At follow-up, the severity of chest pain decreased by 31% (2.63 to 1.83 score points) in LG and 13% (2.37 to 2.09 score points)

Figure 2



Baroreflex sensitivity at baseline and follow-up (mean ± SEM).

in AG (P = .015). The frequency of angina attacks was reduced by 54% in LG, whereas in AG, a slight increase by 11% was found (P = .010). General perceived improvement of QOL was rated higher in LG (P < .001), and the mean physical sum score increased from 43.2 to 48.9 in LG and from 43.2 to 46.1 in control subjects, resulting in a difference of change of 2.9 (95% CI -0.3 to 6.0) (P = .045, adjusted for baseline value). Accordingly, physical function of the 36-Item Short-Form Health Survey improved more in the experimental group (difference 4.3 [-1.2 to 9.9], P = .046, adjusted). Psychological QOL improved comparably in both groups.

Finally, the symptomatic improvement was reflected by a decreased intensity of anti-ischemic medication after 1 year. Although the proportions of treated patients did not change in either group during the study, patients in LG had more frequently reduced their dosage in 30% of

Table III. Medication rates and change of dose during the study according to group assignment

Medication	LG			AG		
	Prescription rate (1 y)	Dose reduction	Dose increase	Prescription rate (1 y)	Dose reduction	Dose increase
ACE/AT-1 RB	24(50)	6(13)	3(6)	26(49)	1(2)	6(11)
Nitrates	19(40)	3(6)	0(0)	24(45)	0(0)	1(2)
Calcium antagonists*	12(25)	5(10)	1(2)	16(30)	0(0)	2(4)
β -Blockers	36(75)	11(23)	4(8)	41(77)	3(6)	6(11)

Values are presented as n (%). $P = .004$ for group difference of dose reductions of the 4 medications. AT-1 RB, Angiotensin-1 receptor blocker.
*Calcium antagonists included verapamil, amlodipine, diltiazem, and nitrendipine.

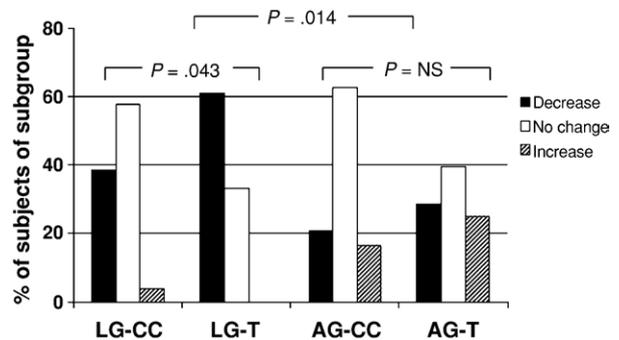
anti-ischemic medications ($P = .004$) (Table III). Nitro spray was used by one third of patients at baseline and remained basically unchanged in both groups. Statin treatment was stopped in 2 LG patients and was newly prescribed in 2 AG patients.

Summarizing the previous results for change in heart rate, HF-HRV, S-SBP, and psychological QOL, the study hypothesis of group differences between LG and AG was confirmed for heart rate only ($P = .005$, Bonferroni-Holm adjusted $P = .02$, all other adjusted $P > .05$).

Lifestyle-gene interaction

Given the only moderate treatment effects despite excellent program adherence, we explored the possibility that the GNB3 C825T polymorphism affected the treatment response. Genotyping yielded 9 TT, 40 TC, and 51 CC genotypes. The baseline data for individuals with homozygous *GNB3**825C/*825C genotype and *825T allele were comparable between groups. The treatment response for coronary calcification, HF-HRV, BRS, and serum lipids was not different between genotypes at the GNB3 locus for the whole study population and within groups. However, heart rate decreased by 1.5 (95% CI -3.7 to 0.7) beat/min in *825T allele carriers but increased by 2.3 (0.3-4.2) beat/min in CC genotypes (net difference 3.8 [0.9-6.6] beat/min, $P = .01$) in the whole study population. Within the linear regression model, only assignment to LG and the presence of the *825T allele were significantly associated with a decrease of heart rate ($P = .002$ and $P = .008$; adjusted for β -blocker use, $P = .0003$, and baseline heart rate, $P < .0001$, $R^2 = 0.41$). In LG, heart rate decreased only in *825T allele carriers by -4.2 (-8.3 to -0.1) beat/min but slightly increased in patients with CC genotype by 0.2 (-2.5 to 3.0) beat/min, resulting in a marginally significant difference between genotypes ($P = .06$).

When further exploring the clinical treatment response in the LG group according to genotype, we found a better reduction of angina in *825T allele carriers (Figure 3). More than 60% of the *825T allele carriers in LG experienced symptomatic improvement. Accordingly, we found an association between genotype and change in physical QOL. Improvement in

Figure 3

Change of severity of angina pectoris (decrease, increase, unchanged) after 1 year in LG and AG according to presence of GNB3 825T polymorphism. Better reduction in angina in LG versus AG ($P = .014$). Within LG, more pronounced improvement of angina in T allele carriers versus homozygous C allele carriers ($P = .043$).

physical function index and presence of the *825T allele were correlated for the whole study group ($r = 0.28$, $P = .005$). *825T allele and the physical sum score tended to be significantly correlated in LG ($r = 0.26$, $P = .072$) but not in AG.

Finally, the treatment effect on the dose reduction of anti-ischemic medication was only significant in *825T allele carriers ($P = .015$) but not in CC genotypes ($P = .3$).

Discussion

This randomized study evaluated the effects of comprehensive lifestyle modification on top of current medical care in patients with CAD. The study hypothesis could be confirmed by showing a significant change in heart rate after adjustment for multiple testing. However, the absolute effect on heart rate was modest and thus may only be of limited clinical importance. Despite excellent adherence to the program, the comprehensive lifestyle intervention had no impact on metabolic risk factors, blood pressure, and 1-year progression of coronary atherosclerosis, as assessed by

EBT. Yet, the lifestyle modification led to a pronounced improvement of autonomic function, as assessed by BRS, accompanied by beneficial effects on anginal symptoms, QOL, and the concomitant need of anti-ischemic medications. As anticipated, the clinical response to comprehensive lifestyle modification was influenced by the GNB3 C825T polymorphism in that *825T allele carriers of LG showed more pronounced effects of the intervention on angina, QOL, and the need of medication.

The dependency of the treatment effect on the GNB3 genotype raises the question on the potentially underlying mechanisms. The *825T allele is associated with enhanced intracellular signal transduction via G protein-coupled receptors.⁶ Moreover, the *825T allele carrier status is associated with a higher risk for hypertension and obesity yet may become only detrimental in conjunction with specific environmental and lifestyle factors.¹⁶ The improvement in symptoms and QOL with the corresponding reduced need of medication may be related to the well-documented dependence of the α -adrenergic coronary vasoconstriction on the C825T polymorphism.⁸ Previous studies have shown that the *825T allele is associated with an increased sensitivity to α_2 -adrenergic coronary vasoconstriction, which adds to the augmentation of α -adrenergic coronary vasoconstriction in the presence of atherosclerosis per se.^{17,18} Because the enhanced G protein activation and sympathetic activation thus are linked to myocardial ischemia, it appears consistent that in our study on coronary patients the *825T allele carriers responded more favorably to lifestyle modification in ischemic symptoms and medication needs.

To our knowledge, no other study has investigated the genetic determination of comprehensive lifestyle treatments in patients with CAD. In healthy younger subjects, it was described that the association between ω -3 PUFA blood levels and endothelial function was dependent on the presence of a Glu298Asp endothelial nitric oxide synthase gene polymorphism.¹⁹ A gene-physical activity interaction between reduction of blood pressure and M235T polymorphism in the angiotensinogen gene was recently reported.²⁰ Our results suggest that the established approach of comprehensive lifestyle modification may be targeted not only to the risk profile but also to the genotype of the patient in the secondary prevention of CAD.

Because our intervention was multifactorial and the study sample size was limited, we cannot specify the interaction between the genetic determination and singular lifestyle factors. As defined in our program and confirmed by analysis of adherence, the major lifestyle change was realized by increased relaxation. Moreover, among the nutritional components, an increase in intakes and blood levels of ω -3 PUFA was apparent. The beneficial effects of the Mediterranean diet are commonly attributed to the increased intake of ω -3 PUFA.

Reductions in heart rate similar to those seen in the present study have been reported with increased consumption of fish²¹ and fish oil supplements,²² and a positive association between HRV and blood levels of ω -3 PUFA from fish oil has been described.²³ However, BRS was not found to be improved by marine ω -3 PUFA in a recent study.²⁴ To date, controlled trials on the effect of Mediterranean diet on cardiac autonomic function are lacking. Nevertheless, in 2 dietary trials focusing on α -linolenic acid (ALA), cardiac death decreased considerably^{25,26} and an increased intake of marine ω -3 PUFA reduced the risk for cardiac sudden death.²⁷ Experimental data suggest that ω -3 PUFA lower the susceptibility to cardiac arrhythmias, mediated by direct effects on the cell membranes of cardiomyocytes or by improvements in cardiac autonomic control.²⁸

Stress reduction may also have mediated the beneficial effects in our study. In prior studies, stress reduction led to a reduction of myocardial ischemia²⁹ and blood pressure.³⁰ To date, no randomized studies have assessed the impact of stress reduction techniques on HF-HRV or BRS.

The lack of effect of the lifestyle intervention on metabolic variables and the progression of coronary atherosclerosis may be explained by improved medical treatment. A marked decrease of progression of the annual Agatston score¹² by statin treatment was reported in a retrospective study and a primary prevention cohort study.^{31,32} The relative annual increase of coronary calcium seen in our study with patients with CAD was in the same order of magnitude. Our lifestyle intervention had no impact on serum lipids, and the low-density lipoprotein cholesterol (LDL-C) levels were higher than now recommended for secondary prevention; however, post hoc analyses revealed no further decrease of coronary calcium progression with lower LDL-C levels. In contrast to our study, patients in the earlier lifestyle trials were mostly not treated with statins and the intervention led to pronounced decreases in LDL-C and small changes in stenoses diameters.¹⁻³ Thus, it seems most likely that, in the presence of statin treatment, a further deceleration of coronary atherosclerosis by intensive lifestyle modification is not feasible, suggesting a floor effect.

Study limitations

Compared with prior studies that evaluated a Mediterranean diet, we found an only modest increase of ALA levels with the diet. Yet, as some ALA is converted to long-chain ω -3 PUFA, we cannot exclude that intakes of ALA were in fact higher than assessed. Furthermore, our patients had to adopt the recommended diet by themselves, whereas in most studies on the Mediterranean diet, key nutrients were delivered to subjects free of charge, thus supporting dietary adherence. Therefore, the dietary changes achieved in our study may better reflect real-life conditions.³³ On the

other hand, compared with more recently evaluated cardiac rehabilitation programs,^{4,5} the SAFE-LIFE intervention achieved better-reported lifestyle adherence. Principally, assessment of adherence by self-report may be biased through overreporting. Whereas the intake of ω -3 PUFA was controlled by biomarkers, we did not measure exercise capacity to verify the effects of exercise. However, we prescribed a rather modest level of exercise (6276 kJ [1500 kcal] per energy expenditure per week) as lifestyle target, which may not be associated with any increased levels of exercise capacity. Also, the lack of weight reduction may be explained by the only modest level of exercise prescribed as well as by the recommended Mediterranean-type diet, which did not result in reduced total energy intakes in our study. To note, also in the Lyon Diet Heart study, the diet had no effect on weight and blood lipids but induced marked beneficial effects on cardiovascular outcomes.²⁵ Therefore, despite the absence of a difference in calcium burden between groups at the present 1 year follow-up, the effect of an intense lifestyle interaction on clinical outcomes may still exist, as such a program might act to lower clinical events through other mechanisms, for example, increased fibrinolytic activity and improved autonomic function.

Electron beam tomography is increasingly used for screening asymptomatic subjects and for primary diagnosis of CAD in symptomatic patients. However, the value of EBT in determination of changing calcium scores that correlate with regression or progression of CAD is currently unclear. Change in coronary stenosis and stabilization of plaques may not correlate with calcium burden. Studies under way and also the pending 3-year follow-up EBT measurements of the present trial will help to clarify the relationship between changes in calcium burden and lifestyle and risk factor modification.

Principally, the moderate sample size of this study limits the statistical power and precludes the finding of small effects, but when effects are found, these are likely to be biologically significant. This report provides a first indication that genetic variation can substantially modulate the beneficial clinical effects of lifestyle modification.

In conclusion, this study demonstrates that comprehensive lifestyle modification in patients with CAD on top of current medical care has no effect on metabolic risk factors and coronary calcification. However, the intervention led to an apparent improvement in autonomic function, paralleled by favorable effects on angina symptoms, QOL, and the reduced need of anti-ischemic medication. The interaction between effects of lifestyle modification and C825T polymorphism is a novel finding, and variation in clinical response to lifestyle treatments may be partly explained by differences in genotype. Genotyping for the C825T polymorphism, thus, could help to better identify

patients with CAD for whom the efforts of rigorous lifestyle modification may be specifically beneficial.

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