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Passive Smoking and Coronary Heart Disease in Women

Prof Dr F. Adlkofer

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Passive Smoking and Coronary Heart Disease in Women

To the Editor:

In a recent article by Kawachi et al,¹ the differing prevalence of cardiovascular risk factors and other lifestyle variables in women with and those without tobacco smoke exposure is attributed to the lower socioeconomic status of the female passive smokers. In order not to impute the socially determined elevated coronary heart disease (CHD) risk to the passive smokers, the authors adjusted their data by standardizing for these factors. In so doing, however, they may have compounded another error, casting serious doubt on the validity of their results. They overlooked the fact that women from lower social classes in general pay far less attention to their health and visit their doctors less frequently than do women from higher social classes. This is particularly true in the United States, where financial reasons also play a role. The exclusion of about 3500 women with a history of CHD before the study commenced, as well as the exclusion of an unspecified number of women with CHD in the course of the study inevitably led to a higher prevalence of undiagnosed CHD cases in the group of passive smokers, so that it is really not surprising that a higher incidence of myocardial infarction was found in the women exposed to tobacco smoke. Given the selection bias, however, a causal relation is not substantiated in this study.

Selection bias is supported also by another finding reported in the article by Kawachi et al. Tobacco smoke exposure at the workplace must have decreased during the study (1982 to 1992) not only for the reasons given by the authors but also because of the aging of the study population. The oldest volunteers who, by virtue of their age were most at risk of developing the disease, were already 61 years old when the study began and, at 71 years of age, had long since retired from the workplace at the time the study was concluded. Despite this ever-decreasing tobacco smoke exposure, the relative CHD risk of passive smokers increased steadily in the course of the study, rising from 1.6 after 4 years to 2.0 after 6 years and eventually to 2.3 after 10 years. This finding, too, is best explained by the selection bias described above. Again, it appears to be justified to assume that there remained from the very beginning and in the course of the study a larger number of women with undiagnosed CHD in the group exposed to tobacco smoke than in the control group. Therefore, passive smoking need not necessarily play a role in this increase in CHD risk.

To support the plausibility of a CHD risk of 1.91 from regular passive smoking, Kawachi et al refer to a study of their own,² which showed a fourfold to fivefold increase in CHD risk in active female smokers compared with female nonsmokers. In other, much better-known studies, such as that of the American Cancer Society Study (CPS II),³ the CHD risk of 1.8 for active female smokers was actually slightly below that reported by Kawachi et al for female passive smokers. Relative CHD risks of active smokers of a similar order of magnitude as shown in the CPS II study have been observed also in the Framingham Study⁴ and in the study on British doctors.⁵ It is difficult to believe that this discrepancy between the CHD risks as found in these major studies on active smokers and the Kawachi et al study can be explained, as Kawachi et al claim, by an increased CHD risk in the control groups because these studies included exposed and

nonexposed nonsmokers, thus narrowing the gap between the CHD risk of smokers and nonsmokers. The credibility of Kawachi and colleagues' hypothesis would improve substantially if the selection bias discussed above were to be excluded. The authors could do this by reporting the number of women with CHD they removed from each exposure group at each time point.

Asked for a possible conflict of interest, I declare categorically that I am not in any way, financially, economically, or otherwise, linked to the cigarette industry.

Prof Dr F. Adlkofer
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A Prospective Study of Passive Smoking and Coronary Heart Disease

To the Editor:

A recent article¹ on environmental tobacco smoke (ETS) and coronary heart disease (CHD) contains conclusions that are not supported by the scientific data.

Among other failings, the data are based entirely on the answer to a single question asked 15 years ago on current "exposure." There is only scant discussion of the subsequent validity of the findings to the present day, in which smoking restrictions in the workplace are very common. Even though the authors used additional questionnaires every 2 years (to assess cardiovascular risk factors and the occurrence of major illnesses), for some reason they did not think it necessary to ever repeat the question on current "exposure." As in virtually all epidemiologic studies on ETS, actual exposure was not determined. However, the surrogate used to assess exposure in this study is especially weak.

Of the 17 multivariate relative risks presented, no less than 11 (65%) could be the result of chance alone, because the confidence interval presented includes the null (in which the disease incidence would be the same in exposed and nonexposed groups). The remaining 6 relative risks have lower confidence limits that are above 1 (and are thus statistically significant), but the associations are extremely weak. The results of the Kawachi study are thus in very close agreement with those from the much larger cohort in the American Cancer Society's CPS-II study.² It is important to note that neither of these two studies shows a statistically significant value for coronary heart disease in women "exposed" to smoke at work. Indeed, the authors of the CPS-II study concluded that their findings "do not show consistent dose-response trends and are possibly subject to confound-

ing by unmeasured risk factors.” The same may well be said of the Kawachi study.

Implausibly, the relative risks presented are only slightly smaller than the value of 1.78 that was reported in CPS-II for CHD in current female smokers aged 35 and above.³

Layard⁴ combined the ETS results of the CPS-II study with two other similar studies to produce a data set with >19 000 CHD cases (compared with 152 cases in the Kawachi study). The pooled relative risk for this data set was 1.00, with a 95% confidence interval of 0.97 to 1.04, a statistically nonsignificant finding that the Kawachi report fails to mention.

The recent statement⁵ “by scientific standards, the weight of evidence continues to falsify the hypothesis that ETS exposure might be a coronary heart disease risk factor” clearly remains valid.

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Passive Smoking and Coronary Heart Disease

To the Editor:

As a cardiologist at work and a passive smoker at home, I read the study of Kawachi et al¹ with more than usual interest. As is often the case with studies of this type, I had some difficulty putting the results in perspective. It is easy enough to figure out that long-term passive smoking approximately doubles one's risk of developing coronary heart disease, but when advising my patients (or my wife) about what their smoking habits are doing to their families and coworkers, it is necessary to use measurements that are absolute, not relative, and that are easily understood by the layperson. One such measurement that I have found useful is days (or hours, weeks, months, and so on) of good health. One may ask, “Based on the data of Kawachi et al, how many days of good health are sacrificed by living or working in a smoke-filled environment?” The data may then be analyzed as follows.

Over the course of 10 years there were 135 coronary events in 25 959 passive smokers. There were 17 events in 6087 nonpassive smokers. Had the latter group been as large as the former (that is, 25 959 individuals), there would have been 72.5 expected events ($17 \times 25\,959/6087$).

When coronary events are plotted against time in years, the area under the curve represents patient-years of good health lost because of coronary disease. If it is assumed that the coronary event rate is a linear function of time, then the 25 959 passive smokers lost $10 \times 135/2 = 675$ person-years of good health during 10 years of follow-up. The normalized group of 25 959 nonpassive smokers lost $10 \times 72.5/2 = 362.5$ person-years of good health. The difference between the two groups is 312.5 person-years, or $312.5/25\,959 = 0.012$ years per person, or 4.4 days per person.

On the basis of the data of Kawachi et al, the average passive smoker loses 4.4 days of good health every 10 years because of coronary heart disease. A reasonable person, looking at the data

expressed in these terms, might conclude that this is a trivial loss notwithstanding the fact that it is statistically significant.

The ability to measure even the tiniest molehill exceedingly accurately does not make it into a mountain.

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Passive Smoking and Coronary Heart Disease

To the Editor:

In the past, Kawachi et al have been deservedly cautious in interpreting their surveys of the Nurses Health Study cohort, but they seem to have thrown caution to the wind in their article, “A prospective study of passive smoking and coronary heart disease” (*Circulation*. 1997;95:2374–2379), as reflected by explosive reports in the news.

In earlier reports by the authors, lack of statistical significance usually prevented conclusions of causality, coupled with a keen concern about confounding and bias. Indeed, this article criticizes other studies that have not adjusted “for the full range of potential confounding factors,” while the authors claim to have adjusted “for a broad range of cardiovascular risk factors”—adjustments that have markedly reduced all crude risks, making most of them not statistically significant. It is not clear, however, what further reductions would have been achieved if the study had also adjusted for other confounders previously identified by the same authors in the same cohort and for which directly applicable data must have been at hand—notably the considerable influence of shift work,¹ weight change,² trans-fatty acid intake,³ and height.⁴ Possibly, such adjustments might have been inconsequential, but the report is silent.

Although the study is said to represent the prospective experience of >32 000 nurses, a scant 152 cases make it comparable to a modest case-control study subject to the uncertainties of a remote one-time determination of exposure, of misclassification, and of clinical verification of markers—inter alia—as the report acknowledges. The authors mention the negative reports from the American Cancer Society and National Mortality Followback Survey databases^{5–7} but resist warning that a nonsignificant risk from their frail database is inconsistent with the no-risk reports from those very much larger databases.

The authors are justifiably troubled in endorsing passive smoking risks substantially greater than the CHD risk attributed to active smoking by the Surgeon General.⁸ In attempting to circumvent the problem, however, they appear to have produced a larger one by arguing that the CHD risk of active smoking is understated because smokers are usually compared with non-smoking control subjects, many of whom are exposed to passive smoking CHD risk. Yet, smokers are also exposed to passive smoking risk at doses and durations far exceeding nonsmoker exposures, which would call for a drastic reduction of the apparent risk attributable to active smoking, assuming the argument and the high passive smoking risks claimed in this report were true.

The article laments the absence of a positive gradient in relation to exposure duration and adduces uncertainties of recall as a reason, but it should be said that the absence of a gradient could very much be real. Also, the authors insist in relating risks to “women,” and although it may be true that all nurses of this cohort are women, not all women are nurses. The authors themselves have documented in almost 100 articles that the women of the Nurses Health Study are quite exceptional and hardly representative of the US female population.

Speculation, of course, is essential and cognoscenti may see through the lines, but feeding such problematic messages to the unwary media challenges responsibility, especially if messages are endorsed by presumed luminaries. Of course, I may be blinded as an occasional consultant to the tobacco industry—still, if there are no answers to the points just raised, perhaps the authors or the *Circulation* editors might consider releasing appropriate cautionary messages to correct what may have become quite unwarranted public perceptions.

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Response

Dr Adlkofer suggests that selection bias could have accounted for our finding of an association between passive smoking and CHD. This possibility is based on two assumptions: that passive smokers were less likely to visit their doctors and receive a diagnosis of CHD, and that excluding women with a history of CHD at the beginning of each follow-up period led to a higher prevalence of undiagnosed CHD cases in the group of passive smokers. We believe that both assumptions are untenable. The Nurses' Health Study participants are all registered nurses and have excellent access to health care. For instance, in 1992 when we asked about the participants' screening behaviors, only 2.4% of the cohort had not had their blood pressure checked during the last 2 years. Moreover, there were no important differences in screening behavior according to passive smoking status. Dr Adlkofer suggested that selection bias was introduced by our exclusion of women with a history of CHD at the beginning of each follow-up period. As we mentioned in our article (p 2375),¹ we did this to avoid potential misclassification caused by women who alter their exposure to passive smoking after developing a major illness and to assess newly incident disease in a population at risk. By using this methodology, 20 medically confirmed cases of CHD were excluded during the 10-year follow-up period. When we repeated the analysis including these 20 cases, the multivariate adjusted relative risk of total CHD among regular passive smokers compared with women not exposed was 1.73 (95% confidence interval [CI], 1.06 to 2.84) compared with the estimate of 1.91 (95% CI, 1.11 to 3.28) published in our article.¹

Both Dr Adlkofer and Dr Coggins question the plausibility of the magnitude of the relative risks we obtained by comparing them with smaller relative risk estimates obtained from other studies of active smoking—for example, the American Cancer Society (CPS II) Study, which reported a relative risk of 1.8 for CHD in female smokers. On this issue, Drs Adlkofer and Coggins were selective in their choice of cited studies; we are aware of just as many cohort studies (eg, the Swedish cohort study by Cederlof et al,² the Rancho Bernardo Study,³ the Finnmark Study,⁴ and our own Nurses' Health Study⁵) that found relative risks of CHD of between 2.6 and 3.6 in female current smokers.

Dr Coggins simply reiterates the limitation that we already acknowledged in our article, that measurement of passive smoking was by self-report and at baseline only. Yet, as we discussed in our article¹ as well as elsewhere,⁶ any resulting random

Medical Screening Behaviors (Percentages Responding They Received It) in the Past 2 Years According to Passive Smoking Status

Screening Behavior	Exposure to Passive Smoking at Home or Work		
	Never	Occasional	Regular
General physical examination	86.8	89.0	88.2
Blood pressure check	97.2	97.6	97.7
Cholesterol check	83.2	84.9	83.7

misclassification of exposure could only change the relative risk estimates in the direction of the null. If misclassification were nonrandom, the “nonexposed” group in our study is more likely to have included passive smokers than vice versa, because people consistently underestimate their exposure to secondhand smoke.⁶ Furthermore, workplace restrictions on smoking became more common during the study period, so that the “exposed” group in our study probably became progressively mixed with women who were no longer exposed. Both types of misclassification push the relative risk estimates in the direction of the null.

Although Dr Coggins questions our use of questionnaire assessment of ETS exposure, he himself places much weight on the study by Layard,⁷ which also used questionnaires completed by surrogate respondents. We did not cite Layard's pooled estimate of relative risks across just three studies because a more thorough meta-analysis incorporating data from 12 studies has been published,⁸ which suggests a statistically significant increase in risk of CHD with passive smoking.

Dr Brennan suggests that studying the risks of passive smoking is analogous to making mountains out of molehills. We were unable to follow the logic of his calculations; however, we would point out that according to credible estimates,⁹ some 35 000 to 40 000 deaths from coronary disease each year may be attributable to passive smoking.

Dr Gori speculates about how our relative risk estimates might have been influenced by adjusting for other risk factors such as height and shift work. As we stated in our article,¹ we adjusted for a very broad range of factors that we determined a priori to be potential confounders. The reason for not adding shift work to our models was that this exposure was not assessed until the 1988 questionnaire,¹⁰ whereas passive smoking was ascertained in 1982. We nonetheless repeated our analysis from 1988 through 1992, including shift work as a covariate. On the basis of 73 cases of total CHD, the multivariate adjusted relative risk among women regularly exposed to passive smoking compared with those never exposed was 2.12 (95% CI, 0.92 to 4.89). This point estimate is quite similar to the relative risk of 1.91 reported in the full study; the width of the 95% CIs reflects the halving of cases caused by shorter follow-up duration. Lacking a sound rationale as to why other variables such as height might act as important confounders in the relation between passive smoking and coronary disease, we believed that it would be pointless to keep adding more variables to our models.

We were puzzled by why Dr Gori refers to the American Cancer Society CPS-II Study¹¹ as a “negative report.” Although two consultants funded by Philip Morris published an analysis of the CPS-II study reporting no association between passive smoking and CHD risk,¹² this report was superseded by a more thorough analysis carried out by the American Cancer Society investigators, which did report a positive association.¹¹

Finally, Dr Gori states that we “have documented in almost 100 reports that women of the Nurses' Health Study are quite exceptional and hardly representative of the US female population.” Although this population was selected for study because

their training and motivation would provide superior data quality, there is no reason to believe that biological relations based on our findings are not relevant to women in general.

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Angiotensin II and Coronary Sympathetic Vasodilation

To the Editor:

Saino et al¹ and Lyons et al² published provocative findings regarding the vascular level interaction of the sympathetic and renin-angiotensin systems. Both authors present possible mechanisms for their observations based on literature evidence and their own observations of the ability of angiotensin to enhance sympathetically mediated vasoconstriction. In addition to the possibilities they presented we would like to suggest that there is the potential that the enhanced vasoconstriction is being mediated by angiotensin per se, which in the presence of catecholamines is being transformed from a subpressor to pressor effect.^{3,4} Such a possibility is consistent with the inhibition of the interaction noted in the presence of perindoprilat.² We would appreciate the thoughts and any observations the authors have with respect to such a possibility.

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Response

There is no question that angiotensin II can play its enhancing effects on the sympathetic nervous system at various levels and that not only a presynaptic potentiation of norepinephrine secretion but also an amplification of the responsiveness of adrenergic receptors to neural stimuli is involved as indicated by the data of Lyons et al.¹ In a study we performed several years ago in humans,² we also suggested this to be the case because in hypertensive patients both acute and long-term ACE inhibition attenuated the reflex increase in forearm vascular resistance due to unloading of cardiac receptors without any concomitant alteration of the reflex increase in plasma norepinephrine.

There is also no question that the enhancing effect of angiotensin II on sympathetic cardiovascular influences is reciprocated because sympathetic nerve activity is an important determinant of renal secretion of renin^{3,4} and thus of the activity of the renin-angiotensin system. It is certainly possible, on the basis of the in vitro findings of Kessler et al,⁵ that this activity is increased by sympathetic influences also because of an enhanced effect of angiotensin II on its receptors. It would be important, however, to devise a way to see whether this is the case also in vivo and what is the relative importance of this mechanism in the overall positive feed-back interaction between the sympathetic and the renin-angiotensin systems.

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1. Lyons D, Roy S, O'Byrne S, Swift CG. ACE inhibition: postsynaptic adrenergic sympatholytic action in men. *Circulation*. 1997;96:911–915.
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Response

Drs Kessler and Kessler suggest that the vasoconstricting effect of angiotensin II may be enhanced by sympathetically mediated vasoconstriction. The suggestion is that higher local concentrations of either angiotensin II or perindoprilat are achieved when a vessel is noradrenergically precontracted by infused norepinephrine or lower body negative pressure. However, the dose of perindoprilat used in our study was not, as suggested by Drs Kessler and Kessler, converted from a subpressor to pressor dose by noradrenergic precontraction as perindoprilat (5 nmol/mL) virtually abolishes the vasoconstricting action

of angiotensin I (200 pmol/min) when coinjected at the brachial artery (unpublished data), though it has no effect on basal forearm blood flow.¹

Finally, submaximal noradrenergic precontraction of a blood vessel is likely to attenuate the vasoconstricting potential of any coinjected vasoconstrictor and thus offset, at least in part, the effect of a local increase in concentration produced by precontraction.

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1. Lyons D, Roy S, O'Byrne S, Swift CG. ACE inhibition: postsynaptic adrenergic sympatholytic action in men. *Circulation*. 1997;96:911-915.

Functional Evaluation of Lipid-Lowering Therapy by Pravastatin

To the Editor:

With great interest we read the article of Dr Aengevaeren and coworkers on further functional aspects of lipid-lowering therapy in patients with coronary artery disease as derived from the REGRESS Study.¹ In comparison to placebo, 2 years of treatment with 40 mg of pravastatin resulting in a decrease of LDL-cholesterol by 23% not only preserved coronary flow reserve (videodensitometric hyperemic mean transit time of contrast media after intracoronary injection of papaverine) but also proved to be superior in respect to its influence on clinical symptoms. Anginal functional class according to the criteria of the Canadian Cardiovascular Society² demonstrated a change of 2.1 ± 0.5 to 1.8 ± 0.8 in the verum versus 1.4 ± 1.0 to 1.7 ± 1.0 in the placebo group, resulting in a mean difference of 0.7 between groups ($P = .03$). Even though the absolute difference in patients treated was not reported to be significant this is the first placebo-controlled trial in patients with stable coronary artery disease, which describes not solely antiischemic properties of LDL-cholesterol reduction as other clinical studies have done previously³⁻⁵ but also supplies evidence for relative antianginal properties when compared to the natural course of the disease over a period of 2 years. As morphologic regression of coronary arteriosclerosis was minimal functional, LDL-cholesterol dependent determinants of coronary blood flow like a decreased coronary vasomotor tone in the epicardial conductance^{6,7} and microvascular resistance vessels⁵ are likely to account for the therapeutic effect.

Another substudy of the REGRESS-Study by Dr Boven and coworkers reported antiischemic effectiveness of the same therapeutic regimen in patients who underwent 48-hour ambulatory ST-Holter monitoring before and after 2 years of treatment.⁴ Unfortunately, even though both studies are presumably derived from the same study protocol, Dr Boven and coworkers did not report the effect of treatment on the functional clinical impairment due to angina pectoris. A variability of the ischemic threshold at the level of the epicardial conductance vessels documented by an increased time to ischemic end points during standardized exercise tests after the intake of fast-release nitrates can be found in at least 30% of the patients with stable coronary artery disease.⁸ It would be interesting to know, whether Dr Boven and coworkers observed a particular benefit of treatment in patients with a variable threshold for the onset of ST-segment depression and anginal symptoms for example defined by a variability in heart rate of >20 bpm at the onset of pathologic changes during the 48 hours ST-Holter recordings.⁹ In case this was true, it would probably prove that lowering of LDL-cholesterol has an absolute and significant antianginal effect when compared with placebo in this subset of patients with a variable threshold of ischemic changes.

Regardless of its beneficial effect in the secondary prevention of coronary artery disease antianginal properties of LDL-cholesterol reduction would have important implications in particular for the treatment of patients with end-stage coronary artery disease and chronic refractory angina pectoris as they are currently subject to studies on various new anti-ischemic interventions such as low-dose intermittent urokinase therapy, spinal cord stimulation, and transmyocardial laser revascularization (see also Reference 10). These patients without a feasible option for successful coronary revascularization are characterized by anginal functional class III or IV resulting in a high rate of anginal episodes (23.4 ± 11.4 episodes/wk) despite maximally tolerated antianginal combination therapy (nitrates, β -blockers, calcium antagonists).¹⁰ If antianginal effectiveness of LDL-cholesterol reduction can be shown based on the considerations mentioned above and if they occurred within a short period as implied by the antiischemic effectiveness after only 3 months of treatment in the study by Dr Gould and coworkers,⁵ this would call for intensified lipid-lowering treatment with documented LDL-cholesterol levels ranging ≈ 100 mg/dL as a necessary precondition before alternative treatment modalities are used.

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Response

The antianginal properties of lipid-lowering therapy by HMG-CoA inhibitors are a potential challenging feature. The basic mechanism of the antianginal effect is not yet completely under-

stood. Although improved endothelial function of epicardial conductance and/or resistance vessels probably is the major contributor to this antianginal effect, antiplatelet activity and decreased blood viscosity might also be properties of additional benefit.¹⁻³

"Whether patients with variable threshold angina pectoris might have an increased benefit over patients with stable angina" is an interesting question, for which we have analyzed the data again. In the ambulatory ECG substudy of REGRESS a reduction of 1.23 episode was found in the pravastatin group versus a reduction of 0.53 episode in the placebo group ($P=.047$).⁴ Patients with ischemia on ambulatory ECG decreased from 28% to 19% in the pravastatin group versus an increase from 20% to 23% in the placebo group ($P=.021$). Total duration of ischemic burden was also significantly reduced by pravastatin as compared with placebo. When we now divide the periods of ischemia in groups with a variability in heart rate of more or less than 20 bpm during ischemia, we found that in the group with a change ≥ 20 bpm, patients receiving pravastatin showed an increase from 1.11 to 1.83 episode per patient ($P=.001$) and patients receiving placebo an increase from 1.27 to 1.96 ($P=.14$), respectively. In patients with ischemic episodes and a difference of < 20 bpm, patients receiving pravastatin showed a reduction from 4.15 to 3.18 ischemic episode per patient ($P=.27$), whereas patients receiving placebo showed an increase from 3.06 to 3.64 episode per patient ($P=.077$). These findings suggest that pravastatin therapy is more effective in ischemic episodes with a low rise in heart rate. These findings support the hypothesis that lipid lowering by HMG-CoA inhibitors has an anti-ischemic effect through an improvement of endothelial function of the coronary (micro) circulation. Most of the episodes of transient ischemia in this study were asymptomatic. The change in angina pectoris classification for this group of patients was not available.

We agree with Dr Schoebel and colleagues that lipid lowering by HMG-CoA inhibitors should be an early step in the treatment of patients with angina pectoris, independent from the cholesterol level to prevent further progression of coronary artery disease. The positive effect on anginal complaints might be advantageous, but at this moment the degree of functional improvement from HMG-CoA inhibitors is largely unknown. Therefore, to state that HMG-CoA inhibitors are a necessary precondition in patients with chronic refractory angina pectoris because of the antianginal properties is questionable. The degree of improvement in myocardial perfusion in absolute terms in the pravastatin group of REGRESS was very limited. It was the placebo group that deteriorated over 2 years of therapy.⁵ These results are in agreement with the LAARS study; in this study patients with extensive coronary artery disease were randomized between LDL-apheresis + simvastatin 40 mg once daily versus simvastatin 40 once daily only. After 2 years of treatment, myocardial perfusion and exercise-induced ischemia improved significantly in the group of patients with LDL-apheresis + simvastatin, whereas patients on simvastatin had no change in myocardial perfusion or exercise-induced ischemia.^{6,7} In this context it is doubtful if HMG-inhibitors in patients with end-stage coronary artery disease and chronic refractory angina pectoris will have a dramatic effect on anginal complaints.

Whether lipid lowering with LDL-cholesterol levels ≈ 100 mg/dL (2.6 mmol/L) are necessary for functional improvement

neither is evident. There are indications that the positive effect of lipid-lowering therapy is not attributed to the degree of lipid lowering but rather to the use of HMG-CoA inhibitors. In the 4S and CARE trial there was no close relation between the degree of lipid lowering and the decrease in major cardiac events.^{8,9} Furthermore, drugs of a total different class may improve endothelial function without lipid lowering.¹⁰

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