patients in our trial had normal serum creatinine at baseline. In the overall study 19% had impaired creatinine clearance at baseline of ≤60 ml/min, and there were no or even numerically worse effects (25% vs. 13%) of NAC on contrast agent-induced nephropathy (CIN) in this specific subgroup—demonstrated in Figure 2 of the publication (1). Performing a clinical trial with selection of patients with elevated serum creatinine ≥140 μmol/l is not feasible, because the serum creatinine is usually not known at hospital presentation and waiting until laboratory results are available is certainly not possible, given the strong relationship of time-to-reperfusion on myocardial salvage (2). Although, overall, there was a 6% CIN reduction by NAC, the lack of effect in patients with impaired renal function raises doubts that there might be effects in different patient groups. Second, regarding the NAC dose, we believe that in total 6,000 mg is a high dose as shown previously (3), and there are currently no clinical trials that have tested higher doses (4). Nevertheless, testing an even higher dose might be worth study. Third, the distribution of NAC between the 2 target organs in our trial is indeed not entirely clear. However, local drug concentration measurement is clinically not feasible, and also local drug application into the renal or the infarct-related artery is considered impractical. Given the fast distribution through the circulation, any relevant impairment of drug distribution is unlikely. Fourth, the 20% reduction in oxidative stress is interesting; however, its effect on clinically relevant parameters such as myocardial salvage or renal function remains unclear. Because the distribution of angiotensin-converting enzyme inhibitors, angiotensin II type 1 antagonists, and statins was similar between both groups (Table 1 of Thiele et al. [1]), effects on oxidative stress are unlikely. Fifth, earlier clinical trials indeed did not use angioplasty, which is the state-of-the-art technique. Sixth, whether the mode of action is dependent on reperfusion type cannot be answered without comparative studies. However, these earlier fibrinolytic trials used much more insensitive surrogate parameters, and the sample size was very small, which raises questions of power.

In general, we agree with Prof. Sochman that our LIPSIA-N-ACC trial should stimulate further research regarding oxidative stress and also a large-scale clinical trial of NAC for CIN prevention. However, we strongly believe, on the basis of our results, that a general application of NAC in infarction patients cannot be recommended.

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Assessing Clinical Utility of Carotid Intima-Media Thickness on the Basis of Reclassification

Although Nambi et al. (1) report significant net reclassification (NRI) with the use of carotid ultrasound of 9.9% in the overall ARIC (Atherosclerosis Risk In Communities) cohort and 21.7% in the intermediate-risk group (5% to 20% 10-year risk) and conclude potential clinical utility in predicting cardiovascular events, the actual NRI tables for those with and without events need to be presented for full assessment of clinical utility. The NRI is determined by: 1) movement to higher risk categories among those with events; and 2) movement to lower risk categories among those without events (2). Although both components of the NRI are of interest, reclassification rates among those with events represent the more clinically relevant measure. However, Nambi et al. (1) do not provide separate reclassification tables for those with and without events to assess where the reclassification is occurring. Furthermore, 2 categories were used for intermediate risk (5% to 10% and 10% to 20%), and it is unclear what drove the net reclassification of 21% within this group: movement to >20% predicted risk in those with events, movement to <5% predicted risk in those without events, or movement within the 2 intermediate risk categories. Showing the actual NRI tables as described by Pencina et al. (2) would aid clinical interpretation. Finally, coronary revascularization and silent MI comprised 43% of the end points analyzed in the ARIC cohort; however, treatment changes would most likely occur for those with events who were reclassified upward to >20% predicted 10-year risk of hard end points alone. Complete assessment of clinical utility on the basis of improved reclassification can only be assessed by showing the full NRI tables for those with and without hard end points.

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Carotid Plaque Assessment

A Bumpy Road to Improved Risk Prediction

We congratulate Nambi et al. (1) on their study of improved prediction of coronary heart disease (CHD) risk by including the information on carotid plaque presence in the ARIC (Atherosclerosis Risk In Communities) study. Inclusion of plaque in the risk prediction model reclassified over 10% of individuals into the higher risk category beyond the levels of carotid intima-media thickness (CIMT) and traditional risk factors. The study is significant because the ARIC investigators acknowledge that small, nonstenotic carotid plaque might be a different phenotype of atherosclerosis, carrying an important contribution to the vascular risk beyond CIMT. Plaque presence was defined if 2 of the following 3 criteria were met: CIMT >1.5 mm, abnormal wall shape, and abnormal wall texture. This is a somewhat novel approach, because Dr. Ward A. Riley (a reputable CIMT and ARIC investigator who unfortunately is no longer with us) believed that "whatever is between intima and media represents CIMT" (Dr. Ward A. Riley, personal communication, 2001). In the recent CIMT meta-analysis (2) very little is mentioned regarding the difference between CIMT and plaque and the prognostic importance of carotid plaque. Carotid plaque is a distinctive phenotype of atherosclerosis, most likely is not a simple continuum of CIMT progression, and predicts stroke and CHD risk better than CIMT (3).

Interestingly, the ARIC investigators report that slightly more subjects were reclassified to a lower risk group (approximately 12%) than to a higher risk group (approximately 11%) after adding CIMT and plaque information. No one was reclassified from the low-risk group (<5% estimated 10-year CHD risk) to the high-risk group (>20% estimated 10-year CHD risk). In the NOMAS (Northern Manhattan Study)—a prospective, multi-ethnic, urban, population-based cohort—the presence of small, nonstenotic carotid plaque reclassified 44% of the low-risk individuals (<10% estimated 10-year CHD risk) to the intermediate-risk category (10% to 20% estimated 10-year risk) (4). In addition, approximately 12% of subjects in a lower risk category had a 10-year estimated risk of 25%, which reclassified these individuals to high risk (>20% estimated 10-year risk). None of the individuals was reclassified to a lower risk category after adding information on plaque presence—as opposed to ARIC. The NOMAS results are, however, hardly ever cited, possibly because they appeared in *Neurology*, a journal mostly neglected by non-neurologists. Therefore, "the intriguing hypothesis" raised by Stein and Johnson in the Editorial Comment (5) that "carotid ultrasound could be used to identify persons at lower than apparent risk who might be candidates for *less* intensive interventions" might be simply rejected if data from NOMAS and others (6) are considered.

Nevertheless, less intensive intervention should not be advised according to ultrasound imaging data for individuals otherwise estimated at intermediate-to-high vascular risk on the basis of traditional vascular risk factors. We believe these individuals should be treated aggressively, irrespective of a possible lower risk according to the information obtained by the levels of biomarkers, either imaging or soluble.

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Reply

We thank Drs. Rohatgi and Berry and Rundek and Salameh for their interest in our communication regarding the use of carotid intima media thickness (CIMT) and plaque to improve coronary heart disease (CHD) risk prediction in the ARIC (Atherosclerosis Risk In Communities) study (1).

It is important to note that our study tested whether CIMT and plaque can help better predict CHD risk, but it does not have the ability to offer guidance on treatment strategies on the basis of such a risk prediction scheme. Therefore, we completely agree with Drs. Rundek and Salameh that, on the basis of our data alone, one should not decide on decreasing interventions. However, we feel that such a strategy should be prospectively tested, as has been suggested by Drs. Stein and Johnson in the editorial that accompanied our publication (2). Drs. Rundek and Salameh also discuss their excellent contribution from the NOMAS (Northern Manhattan Study) (3), in which they examined the value of adding plaque to the Framingham risk prediction score (FRS). However, some important facts/differences need to be considered.