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N-Acetylcysteine Somewhere Between Scylla and Charybdis

Thiele et al. (1) report a study dealing with the impact of N-acetylcysteine (NAC) administered simultaneously on preventing iodinated contrast agent-induced nephropathy and reperfusion injury in patients with ST-segment elevation myocardial infarction treated by percutaneous coronary intervention (PCI). The study included 126 patients compared with a placebo-treated group. Their results as well as conclusions generate many noteworthy associations.

Free oxygen radicals are regarded as variable typically involved either in reperfusion of previously ischemic tissue anywhere in the body or in specific interaction between the iodinated contrast agent and the filtration capacity of the kidney, with the latter being most pronounced with previous kidney injury.

As a result, the exact mode of action of NAC (defense against free oxygen radicals) in the LIPSIA-N-ACC (Prospective, single-blind, placebo-controlled, randomized Leipzig Immediate PercutaneouS coronary Intervention Acute myocardial infarction N-ACC) trial still remains unclear. First, most importantly, it should be taken into account that all patients had normal serum creatinine level, perhaps a crucial fact for further evaluation. A different study design including patients with a priori elevated serum creatinine levels (roughly at least $\geq$140 μmol/l) would be more appropriately representative by making the same size of the patient group sufficient for final statistical analysis. Even so, the incidence of contrast agent-induced nephropathy incidence in the NAC-treated arm of the LIPSIA-N-ACC trial was reported to be lower by 6% when compared with the placebo group. Second, another fact raising some doubt is the selected dose of NAC: 1,200 mg of NAC before PCI cannot be regarded as a high dose even if administered intravenously. In experimental studies, an approximate dose of 100 mg NAC/kg body weight has been used before induction of injury (i.e., this is de facto the total dose of NAC used in the present trial including doses administered within 48 h post-procedurally). Third, likewise, the distribution of NAC between the 2 target organs remains unclear: the kidney exposed to the burden of the iodinated contrast agent versus the ischemic/reperfused myocardium (i.e., the proportion of NAC entering the 2 aforementioned organs and even more so, after recirculation through the pulmonary vessel bed: a Killip class $\geq$2 was reported in 11% of the NAC group and in 14% of the placebo group). The NAC bolus and, actually, the whole dose administered is figuratively somewhere between Scylla and Charybdis, with the former being nephron stress and the latter ischemic and reperfusion myocardial injury. Fourth, the enigma for researchers to be yet resolved continues to be which "high" dose of NAC is actually "high" in terms of being functionally adequate for both the organ compartments in question. The authors (1) report a 20% reduction of oxidative stress markers in the NAC group: this is, however, a biochemical parameter, perhaps not yet reaching a level high enough to have a functional or possibly structural impact on the injured myocardial area. Fortunately enough, almost all patients were receiving angiotensin-converting enzyme inhibitors/angiotensin II type 1 antagonists and statins—hopefully comparable?—in both study groups. Fifth, earlier human studies (for details, see appropriate references in Thiele et al. [1]) used different types of myocardial reperfusion/coronary artery recanalization: fibrinolysis (2) involving opening of the artery by gradual dissolution of a fresh red thrombus, whereas current PCI is "an instantaneous switch for coronary blood flow from the closed to open position." Sixth, the aforementioned makes it unclear whether mode NAC action on the myocardial microvasculature is the same in both reperfusion techniques. Finally, judging by experimental animal studies, NAC seems to exert more beneficial effects on the filtration capacity of the kidney in its more developed injury (3).

The reader could now perhaps say the study simply failed. However, from a scientific point of view, I personally feel this well-designed study has provided many provoking stimuli for further research and definitely is not to be perceived as a breaking point for making indiscriminate decisions in our current clinical practice.

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Reply

We thank Prof. Sochman for his interest in our paper (1) and agree that the exact mode of action of N-acetylcysteine (NAC) for the defense against free oxygen radicals—as shown in our LIPSIA-N-ACC (Prospective, single-blind, placebo-controlled, randomized Leipzig Immediate PercutaneouS coronary Intervention Acute myocardial infarction N-ACC) trial—remains unclear. However, in contrast to the first of 7 statements by Prof. Sochman, not all

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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