REFERENCES

1. Raber L, Juni P, Loffel L, et al. Impact of stent overlap on angiographic and long-term clinical outcome in patients undergoing drug-eluting stent implantation. J Am Coll Cardiol;55:1178–88.
2. Windecker S, Remondino A, Eberli FR, et al. Sirolimus-eluting and paclitaxel-eluting stents for coronary revascularization. N Engl J Med 2005;353:653–62.

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.

***Jan Sochman, MD, PhD**

*Clinic of Cardiology
Institute for Clinical and Experimental Medicine
Videnska 1958/9
140 00 Prague 4 – Krc
Czech Republic
E-mail: jan.sochman@medicon.cz

doi:10.1016/j.jacc.2010.05.032

REFERENCES

1. Thiele H, Hildebrand L, Schirdewahn C, et al. Impact of high-dose N-acetylcysteine versus placebo on contrast-induced nephropathy and myocardial reperfusion injury in unselected patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. The LIPSIA-N-ACC (Prospective, single-blind, placebo-controlled, randomized Leipzig Immediate PercutaneouS coronary Intervention Acute myocardial infarction N-ACC) trial. J Am Coll Cardiol 2010;55:2201–9.
2. Arstall MA, Yang J, Stafford I, Betts WH, Horowitz JD. N-acetylcysteine in combination with nitroglycerin and streptokinase for the treatment of evolving acute myocardial infarction: safety and biochemical effects. Circulation 1995;92:2855–62.
3. Sochman J, Peregrin JH, Bürgelova M, Kopkan L, Kramer HJ, Cervenka L. N-acetylcysteine attenuates iodine contrast agent-induced nephropathy in 5/6-nephrectomized rats. Kidney Blood Press Res 2010;33:149–56.

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