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CORRESPONDENCE

Letters to the Editor

Stent Overlap in Patients Undergoing Drug-Eluting Stent Implantation

I read with interest the paper by Räber et al. (1) comparing patients with multiple drug-eluting stents (DES) in a vessel with overlap with patients with multiple DES in a vessel without overlap and patients with 1 DES/vessel. The authors demonstrated that major adverse cardiac events were more common in patients with DES overlap than in the other groups at 3 years.

First, because the original study demonstrated a significant difference between sirolimus- and paclitaxel-eluting stent groups (2), it would be of great help if the authors would provide data stratified by stent type. Second, overlapping stent implantation was performed for dissection in some cases (28 of 138, 20%). Dissection might be a cause of creatine kinase elevation (myocardial infarction) rather than overlapping stent implantation itself. To clarify this point, it would be of great help if the authors would provide data about peri-procedural creatine kinase elevation and its association with dissection. Third, target lesion revascularization seems to be determined on a per-patient basis. Because there were twice as many lesions/patient (2.0, 394 in 199 patients) in patients with multiple DES in a vessel without overlap compared with the other groups (1.0, 138 in 134 patients; 1.1, 778 in 679 patients), per-patient analysis might overestimate target lesion revascularization rate in patients with multiple DES in a vessel without overlap.

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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 2010;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.

Reply

We appreciate the interest of Dr. Kaneda in our study (1) reporting on the angiographic and long-term clinical outcome in patients with first-generation drug-eluting stent (DES) overlap and take the opportunity to present clinical outcome data up to 3 years stratified/stent type (Table 1) (2). Crude event rates among patients with DES overlap (A), patients with multiple DES in a vessel without overlap (B), and patients with a single stent in a vessel (C) were similar between stent types. Corresponding crude and adjusted hazard ratios (HRs) varied to some extent between stent types, but confidence interval (CI) overlapped widely, and tests for interaction between HRs and stent type were negative, suggesting the absence of a relevant impact of stent type on the clinical outcome among patients with DES overlap.

Dr. Kaneda appropriately raises the question of whether dissections were the source of peri-procedural myocardial infarction (MI) rather than overlapping stent implantations per se. Indeed, peri-procedural MI, defined as any MI occurring within 48 h of the index procedure were more frequent among patients with DES overlap due to dissection (11.1%) as compared with patients with DES overlap related to other indications (0.9%, relative risk: 13.3, 95% CI: 1.3 to 133.0, $p = 0.03$). When excluding peri-procedural MIs from the analyses, however, we found HRs of MI comparing patients with DES overlap and patients with multiple DES in a vessel without overlap similar to those reported in our paper (1): crude HR: 1.30 (95% CI: 0.47 to 3.58); adjusted HR: 2.07 (95% CI: 0.56 to 7.75). Accordingly, dissections might have contributed in part to the observed impact of stent overlap but do not explain the adverse effect emerging during longer-term follow-up in terms of ischemic end points (death or MI) and restenosis.

We concur with Dr. Kaneda that patients with multiple target lesions are more likely to experience target lesion revascularizations (TLRs) than patients with single lesions. In our study, the hazard of TLR was 1.88 times higher in patients with 2 lesions (95% CI: 1.20 to 2.96) and 3.05 times higher in patients with 3 lesions (95% CI: 1.50 to 6.22) as compared with patients with single lesions (p for trend <0.01). We therefore adjusted, as reported in Table 5 of our article (1), analyses for the number of lesions in the multivariable model. The HR of TLR comparing patients with DES overlap and patients with multiple DES without overlap was 1.26 in the crude analysis (95% CI: 0.76 to 2.11), 1.83 in an analysis adjusted for the number of target lesions (95% CI: 1.06 to 3.19), and 1.94 in the fully adjusted analysis reported in Table 5 of our article (95% CI: 1.05 to 3.58) (1).

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Table 1 Clinical Events at 3 Years Stratified According to the Type of Stent Implanted

	Multiple Stents			Crude Analysis			Adjusted Analysis*		
	Overlap (A)†	No Overlap (B)‡	Single Stent (C)§	A vs. B HR (95% CI)	A vs. C HR (95% CI)	p Value‖	A vs. B HR (95% CI)	A vs. C HR (95% CI)	p Value‖
Sirolimus, n = 503									
Total no. of patients	54	102	347						
Death	5 (9.3)	7 (6.9)	22 (6.3)	1.34 (0.43-4.23)	1.47 (0.5–3.87)	0.74	2.86 (0.84–9.68)	1.70 (0.57–5.06)	0.34
Cardiac death	3 (5.6)	5 (4.9)	12 (3.5)	1.13 (0.27–4.73)	1.62 (0.46–5.73)	0.67	2.78 (0.59–13.11)	1.79 (0.42–7.63)	0.43
MI	5 (9.3)	6 (5.9)	14 (4)	1.61 (0.49–5.26)	2.38 (0.86–6.60)	0.24	2.40 (0.59–9.69)	1.52 (0.41–5.60)	0.53
Death or MI	10 (18.5)	13 (12.7)	34 (9.8)	1.47 (0.65–3.36)	1.96 (0.97–3.97)	0.16	2.55 (0.99–6.57)	1.95 (0.85–4.46)	0.11
TLR	8 (14.8)	18 (17.6)	27 (7.8)	0.80 (0.35–1.83)	1.93 (0.88–4.25)	0.01	0.95 (0.33–2.79)	0.86 (0.29–2.51)	0.78
TVR	9 (16.7)	21 (20.6)	34 (9.8)	0.77 (0.35–1.68)	1.75 (0.84–3.64)	0.01	1.07 (0.40–2.86)	0.92 (0.35–2.44)	0.87
Definite stent thrombosis	1 (1.9)	6 (5.9)	10 (2.9)	0.31 (0.04–2.54)	0.64 (0.08–5.00)	0.28	NA	NA	NA
MACEs	13 (24.1)	22 (21.6)	42 (12.1)	1.10 (0.56–2.19)	2.09 (1.12–3.89)	0.01	1.84 (0.80–4.23)	1.57 (0.71–3.45)	0.26
Target vessel failure	13 (24.1)	25 (24.5)	48 (13.8)	0.95 (0.49–1.87)	1.81 (0.98–3.35)	0.02	1.49 (0.66–3.36)	1.43 (0.66–3.08)	0.36
Paclitaxel, n = 509									
Total no. of patients	80	97	332						
Death	8 (10.0)	10 (10.3)	14 (4.2)	0.96 (0.38–2.43)	2.42 (1.02–5.77)	0.04	1.10 (0.38–3.22)	3.82 (1.16–12.57)	0.03
Cardiac death	3 (3.8)	5 (5.2)	12 (3.6)	0.72 (0.17–3.0)	1.05 (0.30–3.74)	0.77	0.72 (0.13–3.91)	1.01 (0.18–5.66)	0.99
MI	6 (7.5)	6 (6.2)	18 (5.4)	1.19 (0.38–3.70)	1.41 (0.56–3.56)	0.75	1.60 (0.40–6.38)	1.94 (0.62–6.11)	0.26
Death or MI	13 (16.3)	15 (15.5)	28 (8.4)	1.03 (0.49–2.16)	1.96 (1.02–3.79)	0.05	1.18 (0.50–2.80)	2.62 (1.10–6.24)	0.03
TLR	19 (23.8)	14 (14.4)	39 (11.7)	1.73 (0.87–3.45)	2.17 (1.25–3.75)	0.02	3.25 (1.45–7.26)	1.47 (0.74–2.91)	0.27
TVR	21 (26.3)	18 (18.6)	47 (14.2)	1.48 (0.79–2.78)	2.01 (1.20–3.36)	0.03	2.84 (1.35–5.96)	1.18 (0.61–2.25)	0.63
Definite stent thrombosis	5 (6.3)	2 (2.1)	12 (3.6)	3.05 (0.59–15.7)	1.79 (0.63–5.08)	0.35	NA	NA	NA
MACEs	21 (26.3)	20 (20.6)	53 (16.0)	1.3 (0.70–2.39)	1.74 (1.05–2.88)	0.09	2.20 (1.08–4.50)	1.31 (0.69–2.46)	0.14
Target vessel failure	23 (28.8)	23 (23.7)	61 (18.4)	1.24 (0.69–2.20)	1.66 (1.03–2.69)	0.09	2.07 (1.06–4.07)	1.09 (0.59–2.00)	0.78

Values are n (%). *Adjusted for diabetes, lesion length, reference vessel diameter, number of lesions, lesion classification, and the presence of acute coronary syndrome. †Patients with multiple drug-eluting stents in a vessel with overlap. ‡Patients with multiple stents in a vessel without overlap. §Patients with a single stent in the vessel. ‖p values for differences in hazards across the 3 groups (A, B, C) in crude and adjusted analyses.

CI = confidence interval; HR = hazard ratio; MACE = major adverse cardiovascular event; MI = myocardial infarction; NA = a multivariable model could not be fitted due to the low number of events and estimated are not available; TLR = target lesion revascularization; TVR = target vessel revascularization.

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.

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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