assessment has been indicated. We would like to remark that, during the second procedure, the right coronary artery engagement and the optical coherence tomography run were successfully performed following a meticulous technique, with no immediate complications (iatrogenic dissection, flow worsening, or flap progression) and with no traces of thrombi formation. Importantly, coronary occlusion was evident, not immediately after this procedure, but 24 h later, following an intense Valsalva effort due to physiological needs. Thus, we think that 2 unique elements did account for vessel failure.

The first element, the presence of a large segment with medial exposure and total occlusion of the true lumen from the right coronary artery ostium. The well-known thrombogenic risk of collagen/smooth muscle cells when exposed to circulating blood, and the disappearance of the medial thromboresistance such as a destruction of its architecture, are features to be considered in large type 1 SCAD. Of note, these characteristics are not invariably present in type 2 SCAD, the most frequent kind (2). The second element, the Valsalva maneuver and subsequent abrupt intrathoracic pressure variations, showed a clear temporal cause-effect relationship in our case and may have produced blood flow velocity changes and shear stress modifications in both true and false lumens.

Finally, definitive evidence on outcomes and optimal treatment strategies in SCAD patients is lacking (3). Some predictors of recurrences have been described (2), but this elusive and challenging scenario warrants further research before one can categorically state which subgroups of patients (i.e., those with large, nude medial coronary segments) may or may not benefit from early invasive or noninvasive re-assessments and interventions.

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Research and Therapeutic Nihilisms in Chronic Kidney Disease

We congratulate Baber et al. (1) for their new analysis of the PROMETHEUS registry. Large real-life registries are critical to confirm the efficacy and safety of new drugs and provide data for key subgroups of patients who are under-represented in clinical trials (CT). Although patients with chronic kidney disease (CKD) compose between 20% and 40% of acute coronary syndromes, they were under-represented in the PLATO (Study of Platelet Inhibition and Patient Outcomes) and TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction 38) trials. In the present study, Baber et al. (1) investigated the real-life outcome of prasugrel compared with clopidogrel in acute coronary syndromes undergoing percutaneous coronary intervention based on kidney function. They identified a lower use of prasugrel in this high ischemic risk population. This is related to therapeutic nihilism, which is well recognized in patients with CKD. Another key result is the lack of significant difference in outcomes after adjustments between prasugrel and clopidogrel (1). However, it should be acknowledged that this lack of significant difference does not imply a lack of benefit of new $P2Y_{12}$-ADP receptor antagonists given the limited power of the analysis and the methodology.

The present study raises critical issues regarding the current trend in CT. In fact, for safety reasons, CT investigating new drugs or interventions often exclude the most severely diseased patients. This not only limits the ability of the intervention to demonstrate superiority but also prevents those who would derive most benefit from these improvements to be eligible for them. Accordingly, CKD remains a cumbersome population with high ischemic and mortality rates (2). In addition, in patients with CKD high on-treatment platelet reactivity is not only associated

with ischemic events but also with mortality (3). The biologic efficacy of prasugrel and ticagrelor in these patients has been confirmed (4). Of importance, a subgroup analysis of PLATO suggested that patients with CKD under ticagrelor had a superior absolute risk reduction than patients without CKD, including a near 30% mortality benefit, without safety issue (2). Unfortunately, this subgroup analysis only enrolled a limited number of patients and none with stage 5 CKD.

Therefore, despite the potential of these new $P2Y_{12}$-ADP receptor antagonists in CKD, clopidogrel remains largely used in clinical practice. New forms of CT including registry-based CT or large pragmatic trials may help to resolve the issue of therapeutic nihilism in research. The TROUPER (TicagRelor Or Clopidogrel in severe and terminal chronic kidney disease patients Undergoing PERcutaneous coronary intervention for an acute coronary syndrome) trial, which will start recruiting in 2017, aims to provide the benefit/risk ratio of ticagrelor 90 mg twice daily compared with clopidogrel 75 mg in patients with stage 4 and 5 CKD undergoing percutaneous coronary intervention for an acute coronary syndrome.

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REPLY: Research and Therapeutic Nihilisms in Chronic Kidney Disease

We thank Dr. Laine and colleagues for their comment on our recent analysis regarding the effect of prasugrel compared with clopidogrel in patients with and without chronic kidney disease (CKD) (1). Indeed, we agree that the conventional design of clinical trials typically excludes high-risk patients with CKD, thereby perpetuating a lack of experimental evidence to inform clinical decisions for such patients. Certainly, pragmatic trials have been used to address other questions in interventional cardiology (2–4) and there is every reason to expect success in studying a CKD patient population. However pragmatic trials may be disadvantaged in the ascertainment of certain endpoints such as bleeding. Furthermore, the issue of unselected consent for randomization in registry-based trials may be regarded as a sensitive matter (5). Nevertheless, these are surmountable problems in view of a just cause, given that CKD accounted for nearly 30% of all acute coronary syndrome percutaneous coronary intervention patients, as we noted in our study.

We agree with Dr. Laine and colleagues that our null findings with respect to differences between prasugrel and clopidogrel may reflect a type II error. Alternatively, preferential use of a more potent agent in lower risk patients might attenuate the expected benefit realized in the controlled setting of a randomized trial. Ultimately, questions surrounding efficacy must be answered by a randomized trial, because registries such as PROMETHEUS are naturally limited by issues of confounding and selection bias. To this end, the positive results reported in the CKD subgroup analysis from the PLATO (Platelet Inhibition and Patient Outcomes) trial are encouraging, but as noted by Laine and colleagues, cautious interpretation is warranted.

PROMETHEUS was successful in representing a large number of patients with CKD undergoing percutaneous coronary intervention for acute coronary syndrome and highlights the therapeutic malaise in prescribing potent therapy to this group. We hope that our results, along with others, focus efforts to pursue evidence-based treatments in patients with CKD.

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