There is an ongoing debate about the role of coronary revascularization in the setting of non-ST-segment elevation myocardial infarction (NSTEMI). American and European guidelines currently agree that an early invasive strategy is recommended in patients with at least 1 high-risk criterion (1,2). However, the optimal treatment strategy for patients with multivessel disease is still unclear. Multivessel disease occurs frequently: it is encountered in approximately 50% of patients with NSTEMI undergoing coronary angiography (3,4). Treatment options include percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery. In coronary artery bypass graft, complete revascularization is the gold standard, but in PCI, 2 important unanswered questions remain: 1) Is complete revascularization superior to culprit lesion-only revascularization? 2) If a percutaneous complete revascularization strategy is chosen, should all lesions be treated in a single session, or should the culprit lesion be treated first, and the residual lesions then be treated in a staged procedure?

In this issue of the Journal, the SMILE (Impact of Different Treatment in Multivessel Non ST Elevation Myocardial Infarction [NSTEMI] Patients) trial provides insight into some of these outstanding issues (5). In this trial of patients with NSTEMI with multivessel disease, all participants underwent complete revascularization. Therefore, no additional information is provided on the benefits or harms of culprit lesion-only revascularization compared with complete revascularization. Unfortunately, the investigators did not report how multivessel disease was defined (e.g., >50% or >70% diameter stenosis), and functional testing of intermediate lesions with fractional flow reserve measurements was not routinely performed. Patients were randomized in a 1:1 fashion to complete revascularization during a single procedure or to culprit-only revascularization, followed by revascularization of the remaining lesions during the index hospitalization after a mean interval of 4.76 ± 1.23 days. The investigators used the radial approach and current-generation drug-eluting stents.

The results were surprising, with significantly lower rates of the primary endpoint of major adverse cardiovascular and cerebrovascular events (defined as cardiac death, death, reinfarction, rehospitalization for unstable angina, repeat coronary revascularization, and stroke) in the 1-stage group at 1-year follow-up. This difference was entirely caused by a higher rate of target vessel revascularization (TVR) in the multistage group. This finding deserves further investigation, because the TVR rate (15.4% at 1 year) in the multistage group was unprecedentedly high in the era of current-generation drug-eluting stents. The only study that comes close to this high event rate is the SYNTAX (Synergy between PCI with TAXUS and Cardiac Surgery) trial, where the 1-year repeat revascularization rate (including TVR, but also non-TVR) was 13.5% in the PCI arm (6). However, in SYNTAX, the mean SYNTAX score was 28, compared with 15 in the current study, and obsolete first-generation paclitaxel-eluting stents were used (7).

Moreover, in SMILE, there were no differences between groups in terms of well-known predictors of
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in-stent restenosis, such as diabetes mellitus, number of vessels treated, lesion length, reference vessel diameter, and so on (8). The event rates start to diverge after 6 months, which is hard to explain when the only difference between the groups was the timing of PCI on nonculprit lesions. To better understand this finding, more information is needed about the type of repeat revascularization. The article only mentions the number of vessels treated, but no information is provided on the number of lesions treated. The SMILE investigators only reported TVR; therefore, it is unclear if the repeat revascularization was for in-stent restenosis (target lesion revascularization) or for a new lesion (non-target-lesion revascularization). Furthermore, no data are provided on the use of invasive or noninvasive testing for ischemia in patients undergoing TVR. The results are counterintuitive, because there is a higher TVR rate in patients whose anatomy is known, where one can plan which lesions to treat in advance and can treat them electively during routine duty hours, rather than in an emergency setting and frequently during off-hours. Until more information is provided to substantiate this finding, it may be best to discard it as an outlier caused by chance.

There were no differences in terms of hard clinical endpoints, such as death and myocardial infarction, between the 2 groups. However, the trial was not sufficiently powered to detect potential differences in mortality between the 2 strategies. The single-stage approach was associated with increased use of contrast medium during the initial procedure (median, 295 ml vs. 180 ml; p < 0.001), but this did not result in higher serum creatinine levels at 48 h after the index procedure or before discharge. It should be noted that patients with an estimated glomerular filtration rate <60 ml/min/m² were excluded from the study. Because of the risks associated with contrast medium use in patients with chronic kidney failure, a staged approach may be preferable in these patients.

In conclusion, when interpreting SMILE, one may find a reason to frown. Many questions remain about the treatment of multivessel disease in patients undergoing PCI for NSTEMI. The unexpected and unexplained finding of increased TVR with multistage complete revascularization deserves further attention.

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