*In reply*

*We note the comments of Drs Sakuma and Morimoto, suggesting caution when interpreting the data in our study published in the* Archives *on June 13.*[1] *Their first point refers to "retrospectively collected" ADE data in our study. This was not the case. Data were collected prospectively at the point of admission, when World Health Organization–Uppsala Monitoring Committee (WHO-UMC) criteria for ADE detection were applied. Only those cases in which WHO-UMC criteria indicated a "probable" or "definite" ADE on admission to hospital were considered by the local expert panel for determination of whether the ADE was causal or contributory to the index hospitalization or an incidental finding. Furthermore, the local expert panel were not aware of whether these patients were taking Beers or STOPP criteria PIMs during their deliberations on the presence or absence of ADEs.*

*Their second point in relation to interpretation of our data suggests that STOPP criteria PIMs might be associated with ADEs due to any drug, not necessarily drugs included in the STOPP list. Drs Sakuma and Morimoto then proceed to mention data of their own, indicating that patients in Japan had a significantly higher risk of ADEs if they were prescribed STOPP or Beers criteria PIMs, although the ADEs in question may not be attributable to the identified STOPP or Beers criteria PIMs. The implication here is that STOPP and Beers criteria may be indicating ADE risk in general, not necessarily ADEs specifically attributable to PIMs listed in the 2 sets of criteria. In our study, we analyzed the number of consensus panel–identified ADEs (n=329) that were simultaneously cited in STOPP and Beers criteria; 170 of 329 ADEs (51.7%) were cited in STOPP criteria compared with 67 of 329 ADEs (20.4%) cited in Beers criteria. This means that ADEs were identified 2.55 times more frequently in STOPP than in Beers criteria, a significant difference. Furthermore, the number of ADEs deemed causal or contributory to index hospitalization and simultaneously avoidable or potentially avoidable was 151; 94 of these 151 ADEs (62.2%) were identified by STOPP criteria compared with 34 of 151 (22.5%) identified by Beers criteria, another significant difference between STOPP and Beers criteria.*

*We agree with Sakuma and Morimoto's point that the utility of STOPP for prevention of serious ADEs in older people remains uncertain. This question is currently being addressed in a randomized controlled trial.*

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## Percutaneous Coronary Intervention for Persistent Occlusion of the Infarct-Related Artery: An Expanded View of the Evidence

Deyell et al[1] provide evidence that the rate of percutaneous coronary intervention (PCI) for an occluded infarct-related artery (IRA) more than 24 hours after acute myocardial infarction (MI) has not significantly changed since publication of the Occluded Artery Trial (OAT).[2] Their article, however, fails to address published evidence from several articles that provides some supportive evidence for performing PCI late in the course of an acute MI.

Abbate et al[3] performed a meta-analysis of 10 randomized trials comparing late PCI with medical therapy (including the OAT) in the setting of acute MI and showed an overall survival benefit favoring PCI. There was also a significant improvement in left ventricular ejection fraction and reduced cardiac volumes. Appleton and colleagues[4] restricted their meta-analysis to only include trials with persistent total occlusion of the IRA, showing that PCI was associated with a statistically significant improvement in LVEF and cardiac remodeling.

Long-term outcomes from the Beyond 12 hours Reperfusion Alternative Evaluation (BRAVE-2) study[5] were recently published, showing that stable patients with acute MI randomized to PCI between 12 and 48 hours from symptom onset had significantly improved survival 4 years later compared with medical therapy alone. The mortality rate in the PCI arm was 11.1% compared with 18.9% in the conservative arm ($P=.047$). The rate of subsequent revascularization was also lower with PCI (25.8% vs 69.1%; $P<.001$).

We have previously expressed concerns regarding the appropriateness of changes made to PCI guidelines.[6] Patients who present late with an acute MI are a heterogeneous population, and the clinical decision regarding PCI should not be the same for all. We suggest that those who are still early in the course of an MI (12-48 hours) should undergo PCI. Those beyond 48 hours with evidence of silent ischemia or viability should also undergo PCI. Patients who are truly stable and asymptomatic beyond 48 hours from symptom onset, with no evidence of silent ischemia or viability, can safely be treated with medical therapy. While it is important that patients do not undergo invasive procedures that are not likely to have any benefit, we should also not withhold these therapies from the subgroups of patients who do stand to benefit. We hope that these new data will spur renewed interest in the larger body of evidence evaluating PCI in this setting

and that the guidelines for this heterogenous population are expanded to consider different subgroups of patients who present late with acute MI.

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### *In reply*

*We agree with Appleton et al that "Patients who present late with an acute MI are a heterogeneous population"; the OAT results do not apply to all. It is precisely this heterogeneity that makes conclusions from the meta-analysis by Abbate et al[1] invalid. That analysis did not restrict itself to patients with total occlusions late after MI, but rather included patients with closed* and *patent IRAs.[2] The meta-analysis that restricted itself to post-MI patients with total IRA occlusion showed no benefit from routine PCI.[3] It is this subset to which the updated guideline recommendation applies.*

*The BRAVE-2 evaluated only 352 patients; of the subset with angiograms, only half had IRA occlusion. Those authors noted the risk of type 1 error, with their results as hypothesis generating. The OAT provides robust long-term outcomes (≤9 years; mean, 6 years) in 2201 patients with total IRA occlusion more than 24 hours after MI without rest angina, severe inducible ischemia, severe heart failure, or left main or 3-vessel disease.[4] Death, MI, and heart failure were not reduced by PCI, with consistent findings for those enrolled 3 days or less or with any high-risk variable. The OAT data are hypothesis testing, not hypothesis generating.*

*We reported methodological concerns regarding some analyses of left ventricular indices.[2] Among 389 OAT patients with paired core laboratory measurements, 1 year ejection fraction (EF) was improved in 66%, whether they were assigned to revascularization or medical therapy.[5,6] When clinical outcome data are available, surrogate end points provide interesting insights but little clinical guidance.*

*The suggestion that viability identifies a subgroup who benefit from PCI is unfounded. In an OAT ancillary study, approximately 70% had at least moderate viability in the infarct zone[6] with no interaction with treatment assignment; this is consistent with the EF increase data cited in the preceding paragraph. The Surgical Treatment for Ischemic Heart Failure (STICH) trial found no interaction between the effect of revascularization on death or cardiovascular hospitalization whether viability was present or not.[7] Observational studies linking viability to EF improvement after revascularization did not have a randomized comparator group and were not conducted with current medical therapy.*

*What then is the important heterogeneity that the OAT highlights for thoughtful clinicians? We submit it is the distinction between closed vs patent IRAs in stable MI survivors. The natural history and response to PCI of persistent IRA total occlusion is different from that of a patent IRA, which harbors unstable plaque. The former cannot easily worsen; the latter is an invitation for rethrombosis. The American College of Cardiology/American Heart Association guidelines do recognize this heterogeneity, and it is past time for clinicians to follow suit.*

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