In this issue of Circulation: Cardiovascular Interventions, Wang et al.\(^1\) publish on the real-world impact of platelet function testing where clinicians have direct access to point-of-care platelet function testing without protocol-mandated treatment strategies. Their hypothesis was that no-cost access to platelet function testing would increase treatment adjustment with P2Y\(_{12}\) receptor inhibitors and subsequently improve clinical outcomes of acute coronary syndrome (ACS) patients. Their conclusion is that access to no-cost platelet function testing had a modest impact on ADP receptor inhibitor selection and dosing and no impact on clinical outcome. Strikingly, switching from clopidogrel to more potent P2Y\(_{12}\) receptor inhibitor seemed to be independent of platelet function test results. The Treatment With Adenosine Diphosphate Receptor Inhibitors: Longitudinal Assessment of Treatment Patterns and Events After Acute Coronary Syndrome Prospective Open Label Antiplatelet Therapy (TRANSLATE-POPS) is a relevant study as it brings into light how evidence-based medicine is translated into the real-life setting.\(^1\)

### See Article by Wang et al

This study first outlines the disproportionate relationship between knowledge and implementation into clinical practice. TRANSLATE-POPS was a prospective, cluster-randomized trial where participating centers were assigned access to no-cost platelet function testing versus usual care for ACS patients treated with PCI. Platelet function testing was performed only in two-third of patients treated in intervention sites. More importantly, treatment adjustments occurred in <20% of patients despite prior evidence that in such context at least one-third of patients would have deserved intensification of P2Y\(_{12}\) inhibition as a consequence of on-treatment high platelet reactivity.\(^2,3\) The fact that treatment decisions in response to measurement were at the discretion of the treating physician without formal guidance is a first plausible explanation. The lack of rigorous validation that platelet function testing improves patient outcomes and are demonstrated to be cost-effective is also a strong driver for such discrepancy.\(^4\) This is further reflected by the guidelines that have given a class IIb recommendation for platelet function testing or genotyping if the results of testing may alter management.\(^5\) In other words, this approach should be restricted to clinical research or unexpected situations but not be routinely used.

The second most striking finding of the TRANSLATE-POPS is that clopidogrel was the predominantly used P2Y\(_{12}\) inhibitor in an ACS population treated by percutaneous coronary intervention, a situation where more potent P2Y\(_{12}\) inhibitors have demonstrated a mortality benefit as compared with clopidogrel.\(^6\) The slow uptake of prasugrel and ticagrelor remains a concern for which the most likely explanation is the availability of generic clopidogrel which can be <10% of the cost of more potent P2Y\(_{12}\) inhibitors. Although clopidogrel remains the leading drug sold worldwide to avoid stent thrombosis, its nonselective administration remains counterintuitive in an ACS patient population when a measurable drug effect is mandated and when there is the possibility to identify patients at risk of developing adverse outcomes that can be prevented. In addition, despite clopidogrel carries a genomic label by the Food and Drug Administration, meaning that there is a recommendation for genotype assessment before the drug is used, there is rarely any pharmacogenomics assessment in clinical practice.\(^7\) The question arises why there are such gaps and where to go now?

We are leaving in a world where continuous tracking is now obtainable for most key physiological metrics. Refinements that are actively being pursued also include point-of-care platelet function test and genotyping to make this much more rapid and inexpensive. There is hope and room for improvement. In the Genotyping Infarct Patients to Adjust and Normalize Thienopyridine Treatment trial (GIANT, NCT01134380), genotype-guided antiplatelet therapy after primary percutaneous coronary intervention was evaluated and use of prasugrel was strongly recommended in carriers of the CYP2C19 clopidogrel loss of function allele leading to a similar 1-year composite risk of ischemic events as compared with noncarriers on clopidogrel. Although the use of genotyping was not randomized, it demonstrates that point-of-care genetic testing is feasible to refine treatment strategy in high-risk patients. The ongoing Cost-Effectiveness of CYP2C19 Genotype Guided Treatment With Antiplatelet Drugs in Patients With ST-Segment–Elevation Myocardial Infarction Undergoing Immediate PCI With Stent Implantation: Optimization of Treatment (POPular Genetics) trial is now testing this hypothesis in 2700 ST-segment–elevation myocardial infarction patients randomized to a CYP2C19-guided genotype therapy or a conventional therapy to improve net clinical benefit.\(^8\)

The way trials are designed is critical to avoid lost in translation of personalized medicine. Although TRANSLATE-POPS
used a pragmatic cluster-randomized design, it was under-
powered to detect differences in outcomes between strat-
gies because of a lower than expected penetration of platelet function testing. In the TRIGGER-PCI trial, one-third of the enrolled patients declined randomization after being identified as having high platelet reactivity further outlining the limitation of a strategy of identification of deemed nonresponders instead of randomizing the use of platelet function testing and adjust-
ing treatment.9 The low-risk population and the lack of strong pharmacological intervention were the major drawbacks of the Gauging Responsiveness With a VerifyNow Assay—Impact on Thrombosis and Safety (GRAVITAS) trial.10 This highlights the need for considering different study designs with more appropriate population risk level, cutoff value used to define platelet reactivity and outcome definitions.

The goal of personalized medicine is to focus on patients in whom the one size fits all approach does not apply easily but in whom the benefits derived from megatrails can be important and validated for the individual patient. This is the objective of the ongoing ANTARCTIC study (Assessment of a Normal Versus Tailored Dose of Prasugrel After Stenting in Patients Aged >75 Years to Reduce the Composite of Bleeding, Stent Thrombosis and Ischemic Complications; ClinicalTrials.gov number, NCT01538446) that is evaluating the superiority of a strategy of platelet function monitoring with dose and drug adjustment in patients initially treated with prasugrel 5 mg as compared with a conventional strategy using prasugrel 5 mg without monitoring and drug adjustment in ACS patients aged ≥75 years.11 For the first time the concept of a therapeutic window of P2Y12 inhibition is being tested and the outcome is the net clinical benefit, a combination of Bleeding Academic Research Consortium 2, 3, and 5 bleedings and ischemic end points that is more relevant in such peculiar patient population.

Disclosures
Dr Collet reported receiving research grants from Bristol-Myers Squibb, Sanofi-Aventis, Eli Lilly, Medronic, and Boston Scientific; consulting fees from Sanofi-Aventis, Eli Lilly, and Bristol-Myers Squibb; and lecture fees from Bristol-Myers Squibb, Sanofi-Aventis, Eli Lilly, and AstraZeneca. Dr Silvain reported receiving research grants to institution from AstraZeneca, Sanofi-Aventis, Boehringer-Ingelheim, Daiichi-Sankyo, Eli Lilly, Brahms, INSERM, Fédération Française de Cardiologie, and Société Française de Cardiologie; consultancy fees from AstraZeneca, Bristol Myers Squibb, Daiichi-Sankyo, Eli Lilly, The Medicines Company; and lecture fees from AstraZeneca, Boehringer-Ingelheim, Cordis, Daiichi-Sankyo, Eli Lilly, Iroko Cardio, Stentys, and Servier. Dr Montalescot reported receiving grant support from Abbott Vascular, Boston Scientific; Cordis, Eli Lilly, Fédération Française de Cardiologie, Fondation de France, Guerbet Medical, INSERM, ITC Edison, Medtronic, Pfizer, Sanofi-Aventis, Société Française de Cardiologie, and Stago; consulting or board fees and lecture fees from AstraZeneca, Bayer, Boehringer-Ingelheim, Cardiovascular Research Foundation, Cleveland Clinic Research Foundation, Daiichi-Sankyo, Duke Institute, Eli Lilly, Europa, Lead-up, GlaxoSmithKline, Institut de Cardiologie de Montréal, Menarini, Nanospheres, Novartis, Pfizer, Portola, Sanofi-Aventis, the Medicines Company, and the TIMI Study Group.

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