Patients who experience an acute coronary syndrome (ACS) are at increased risk for additional ischemic events across vascular territories. This risk is modifiable, with randomized controlled trials (RCTs) demonstrating the efficacy and safety of several types of interventions in patients with prior myocardial infarction, including antithrombotic agents, lipid-lowering therapies, and nonculprit lesion revascularization in the case of hemodynamically stable ST-segment–elevation myocardial infarction.

Some of the heightened risk following ACS is attributable to the culprit lesion itself, although many recurrent events are unrelated to the index ACS lesion, vessel, or even vascular bed. This distinction takes on particular salience in the case of patients who undergo percutaneous coronary intervention (PCI) for the index ACS, as these patients remain at risk for nontarget lesion events and are also at risk for stent-related complications, most notably stent thrombosis.

With respect to antiplatelet therapy, PLATO (Study of Platelet Inhibition and Patient Outcomes) and TRITON-TIMI (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel–Thrombolysis in Myocardial Infarction) were large RCTs showing greater efficacy of the third-generation P2Y12 inhibitors ticagrelor and prasugrel than clopidogrel in patients with ACS treated with aspirin. PLATO enrolled 18,624 patients with ACS who were randomized to ticagrelor, 90 mg twice daily, versus clopidogrel, 75 mg daily, and followed up for 12 months. The rate of major adverse cardiovascular events was 16% lower in patients assigned to ticagrelor, including a lower rate of all-cause mortality. Rates of bleeding were higher with ticagrelor.

Concerning the subset of ACS patients who undergo PCI, the efficacy of ticagrelor in PLATO was consistent in patients with a planned invasive strategy (71% of total population), including a 19% reduction in all-cause mortality and a 36% reduction in definite stent thrombosis. In TRITON-TIMI 38, in which 99% of patients underwent PCI (95% received a stent), definite or probable stent thrombosis was reduced by 52% with prasugrel.

The superior efficacy and acceptable safety profile of ticagrelor and prasugrel have led to major society guidelines favoring these agents over clopidogrel in most patients with ACS, including those treated with PCI.

Although large, well-conducted RCTs are the mechanism by which to assess the efficacy and safety of one intervention compared with another, they obviously do not answer every question relevant to the use of these medications in daily practice. Cardiovascular trials typically enroll white men in their 60s from North America and Western Europe, raising legitimate questions about generalizability to more diverse populations and
clinical scenarios. Furthermore, societal considerations, such as cost-effectiveness, are simply beyond the scope of a trial designed to understand the efficacy and safety of a drug, device, or therapeutic strategy in a specific patient group or disease state. For these reasons, “real-world” data have the possibility of providing important adjunctive insight into how the internally valid findings of a well-executed trial translate into the external world.

In this spirit, Völz and colleagues have explored, in this issue of the Journal of the American Heart Association (JAHMA), the use of ticagrelor versus clopidogrel in patients with ACS treated with PCI using data from the SCAAR (Swedish Coronary Angiography and Angioplasty Registry). The authors captured information pertaining to all PCIs performed in the setting of ACS at 5 hospitals in a single region of western Sweden over a 10-year period (2005–2015) and compared outcomes in patients treated with ticagrelor with those in patients treated with clopidogrel. The primary end point for this comparison was the composite of all-cause mortality or stent thrombosis at 30 days. The association between antiplatelet therapy and subsequent outcomes was adjusted on the basis of clinical and procedural characteristics using instrumental variable 2-stage least squares regression.

A total of 12,168 patients were treated with clopidogrel during the specified time period, and 2929 were treated with ticagrelor. As would be expected, the proportion of patients treated with ticagrelor increased over time. Patients treated with ticagrelor more frequently had prior myocardial infarction, prior PCI, and prior bypass surgery, whereas patients treated with clopidogrel more commonly presented with non–ST-elevation ACS and cardiogenic shock. Drug-eluting stents, invasive physiologic lesion assessment, and intracoronary imaging were more commonly used in patients treated with ticagrelor, presumably at least in part reflecting secular trends in these procedural characteristics.

There was no difference in the adjusted odds of death or stent thrombosis at 30 days between patients treated with ticagrelor and those treated with clopidogrel. Patients receiving ticagrelor had higher rates of in-hospital bleeding. There continued to be no significant association between initial therapy choice and all-cause mortality at 1 year.

So, what lessons can we draw from these observational comparisons in a setting in which we already have large randomized trial data? Rephrased, in what ways does this analysis help translate the existing efficacy and safety data for ticagrelor into the “real world”?

First, SCAAR is a comprehensive registry and allows for a reasonably complete description of the transition from clopidogrel to ticagrelor in a broad healthcare system. From the first month in which ticagrelor was prescribed, March 2012, it was only 2 months until ticagrelor became the dominant P2Y12 inhibitor. This observation highlights the rapid translation of guidelines and health system–level decisions to patient-level care in systems such as Sweden’s and therefore speaks to the importance of analyses such as the one by Völz et al. The rapid transition and relative homogeneity of prescribing patterns also speaks to the fundamental biases present in observational analyses. As the authors note, only 30% of this cohort was treated after ticagrelor became the default P2Y12 inhibitor, and of these, only 35% were treated with clopidogrel. Therefore, only about 11% of patients in this analysis received clopidogrel as a real “choice” or “alternative” to ticagrelor. The greater the imbalance between the rates of use of each therapy, the greater concern there is for important unmeasured confounders driving the observed associations.

Second, although this analysis does still rely on a demographic similar to the original PLATO trial, there is an important difference in age. Only ≈15% of patients enrolled in PLATO were at least 75 years of age, whereas nearly 30% of patients in the present analysis were >75 years of age. The median age is about 68 years, which reflects current clinical experience in North America and Europe. As such, there may be important differences in bleeding and ischemic risk in this cohort compared with PLATO. The bleeding rates are difficult to compare given the evaluation of only in-hospital bleeding here, but the absolute rates of all-cause mortality and the composite of death, myocardial infarction, or stroke at 1 year are higher in the SCAAR analysis than in PLATO.

An important limitation is the lack of data on treatment discontinuation. Even in RCTs, there have been appreciable rates of ticagrelor discontinuation, and one might conjecture that crossover from ticagrelor to clopidogrel would make these 2 treatment strategies more similar in the “real world” than in the setting of an RCT. This is an important hypothesis raised by this analysis.

It is also relevant to note the low rates of drug-eluting stents, physiologic assessment, intracoronary imaging, and complete revascularization relative to current guidelines and practice, reflecting the overall time period of assessment. Given that these approaches have demonstrated clinical benefit, one might hypothesize that in the modern era there may be less anticipated benefit from potent antiplatelet therapy than has been true historically. This is, of course, speculative, but optimized PCI is evolving rapidly and it is not unreasonable to expect these changes to impact residual risk and, therefore, the absolute marginal benefit of adjunctive medical therapy in the future.

Is there direct clinical application of these findings? As the results presented here are observational, they are vulnerable to important unmeasured confounders. That said, these observations provide an essential
reminder for clinicians that many patients encountered in daily practice do not neatly fit the populations and clinical scenarios investigated in RCTs and careful, patient-centered decision making is required. In particular, the findings here raise valid questions about therapeutic strategy in patients who are older or may be less likely to maintain long-term ticagrelor therapy following PCI for ACS.

In conclusion, Völz and colleagues have examined the use of ticagrelor and clopidogrel in actual clinical practice in Sweden, making important observations about current management of patients with ACS treated with PCI. In so doing, they have raised relevant hypotheses warranting further investigation. Intraprocedural techniques and antithrombotic strategies following ACS and PCI are evolving quickly, with significant promise for impact on long-term clinical outcomes. In the meantime, these 2 trends are playing out in everyday clinical practice: comprehensive data sets, such as SCAAR, provide an invaluable resource as we aim to understand the translation of RCT data into actual patients’ lives.

ARTICLE INFORMATION

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