The unequivocal importance of platelet inhibition for prevention of secondary occlusive vascular events in patients with coronary heart disease is well established. Yet the scientific debates on the preferred agents for platelet inhibition have reached new heights. Recent antiplatelet clinical trials, such as Aspirin and Clopidogrel Compared With Clopidogrel Alone After Recent Ischaemic Stroke or Transient Ischaemic Attack in High-Risk Patients (MATCH), Clopidogrel and Aspirin Versus Aspirin Alone for the Prevention of Atherothrombotic Events (CHARISMA), Therapeutic and Aspirin Versus Aspirin Alone for the Prevention of Non-–ST Elevation Myocardial Infarction (ACCOAST), and Platelet Inhibition and Patient Outcomes (PLATO), have raised concerns with regard to vascular anti-thrombotic efficacy in the investigated, more potent combination antiplatelet regimens, which at the same time increase the bleeding risks. In a different conceptual approach, researchers have attempted to link high-risk cohorts and worsened clinical outcomes to the degree of platelet inhibition by individual tailoring of antiplatelet therapy. However, trials, such as the Gauging Responsiveness With A VerifyNow Assay—Impact on Thrombosis And Safety (GRAVITAS), Testing Platelet Reactivity In Patients Undergoing Elective Stent Placement on Clopidogrel to Guide Alternative Therapy With Prasugrel (TRIGGER-PCI), Intravenous and Oral Administration of Elinogrel to Evaluate Tolerability and Efficacy in Nonurgent Percutaneous Coronary Intervention Patients (INNOVATE-PCI), Assessment by a Double Randomization of a Conventional Antiplatelet Strategy Versus a Monitoring-Guided Strategy for Drug-Eluting Stent Implantation and of Treatment Interruption Versus Continuation One Year After Stenting (ARCTIC), The Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes (TRILOGY-ACS), and A Comparison of Prasugrel at PCI or Time of Diagnosis of Non––ST Elevation Myocardial Infarction (ACCOAST), did not lend support to this notion. Lately, some differentiations emerged, for example, the insight by Salisbury et al who have shown that the expected benefits and risks of prasugrel versus clopidogrel may depend on underlying patient characteristics. This may be the first step toward an individualized selection of antiplatelet regimen, allowing to maximize benefits and diminish risks of such agents based on risk modeling.

As with every novel pharmacological principle, documentation of real-life contemporary use of antiplatelet therapy is of utmost importance, aside from the experience gained in randomized trials. In this sense, the article by Sandhu et al (see page 293 of this issue) fills an important gap. This study is a timely and well-designed prospective registry of almost 56,000 consecutive patients with percutaneous coronary intervention. The strengths of the article are large sample size of patients treated with prasugrel (almost 10,000), and a uniform outcome assessment within the Blue Cross Blue Shield framework of the 34 hospitals Cardiovascular Consortium. The limitations of the article are the absence of 2012 outcome data, when the actual prasugrel US expansion occurred, and lack of pivotal safety data, such as bleeding and cancer rates, during prasugrel therapy compared with clopidogrel. The potential cancer risks during prasugrel therapy in TRITON generated an ongoing animated debate. Excess of solid cancers occurred early (already at the first month in women and with a 4-month delay in the overall TRITON population) without any obvious biological explanation. These signals are certainly not caused by prasugrel per se but can be attributed to the stronger platelet inhibition, that is, demasking microbleeds in cancers or (although less likely) conferring an inability to combat undifferentiated cancer cells in situ. If these are valid observations, the occurrence of solid cancers may be easily captured even in short-term registries, and such emerging data will be extremely valuable for clinicians.

The focus of the article by Sandhu et al is on true indications and contraindications. Regarding the first, it is clear that one has to be critical to the use of a new medication outside of its documented indications. Importantly, the study reports that real-life prasugrel use for non-acute coronary syndrome indications was as high as 28.3%. Furthermore, the authors found a steady increase in prasugrel use, with ≈22% of patients undergoing percutaneous coronary intervention on this therapy by study end. It is disquieting that prasugrel contraindications have been ignored with a surprising frequency. This is not a sign of good clinical care and meticulous handling of potent pharmaceuticals. Indeed, the authors do have a point in asking for quality assurance systems. Responsibility rests on the manufacturers of new pills as well, which they are aware of, usually providing clear and comprehensive instructions to every potential prescribing physician with regard to correct indications and precise contraindications.
There may be a type of a spill-over phenomenon in play based on mechanisms that encompass, eg, extrapolation from different medications. In this particular case, if physicians are used to prescribing clopidogrel to patients without acute coronary syndrome, then their switch to prasugrel may erroneously lead to the same prescription pattern. Such utilization may be motivated by reports that document more homogenous platelet inhibition of prasugrel as compared with clopidogrel, even in cohorts that have been tested for CYP2C19 genotype variations.

There are practical opportunities to improve quality of prescription of new drugs. Electronic systems that are incorporated into patient chart software, used for filling prescriptions by electronic means, may be potentially helpful. They might catch situations in which contraindications are not addressed adequately or alert the prescribing physicians in case indications are not followed.

Clinical utilization of prasugrel is growing now but will face some serious challenges. First, the recent TRILOGY-ACS trial in noninvasive medically managed patients showed no advantage of prasugrel over clopidogrel. Negative results of this trial will most likely preclude further expansion of prasugrel beyond present indications. Second, the prasugrel patent will expire in 2017, making it highly unlikely that any other outcome-driven trial will be done with this agent. Therefore, contemporary registries from now on will represent the best available evidence in assessing the risk/benefit profile of prasugrel.

Disclosures

Dr Serebruany is listed as an inventor and received compensation for the issued US Patent “Method for treating vascular diseases with prasugrel” assigned to Lilly. He received funding for research studies with both prasugrel and clopidogrel. Dr Atar has received speakers honoraria from Astra-Zeneca and Sanofi-Aventis.

References


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Victor Serebruany and Dan Atar

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