

Ticagrelor after Acute Coronary Syndrome: One For All or Part of Personalized Medicine?

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Dual antiplatelet therapy (DAPT) with acetylsalicylic acid and a P2Y₁₂ receptor inhibitor is indispensable for prevention of ischemic complications in patients with coronary events or after stent placement. Both third-generation P2Y₁₂ receptor inhibitors, with earlier onset of action, as well as greater and more consistent level of inhibition without the annoying interindividual variability in non-responding to ADP inhibition, were found superior to second-generation P2Y₁₂ inhibitor clopidogrel.^{1,2}

These advantages seen in guideline-changing trial are not reflected in a recent registry; PLATO and other randomized controlled trials (RCT) might not depict the real-world high-risk setting as convincingly shown in the work by Gro Thrane et al in this issue of *The Lancet Regional Health - Europe*.⁴ The authors overcome elegantly the randomization and selection bias by carrying out a pre-post two cohort analysis of the mandatory Western Denmark Heart Registry and the Danish Health Registry. They compared a 4-year period before introduction of ticagrelor (2007-2010; n=7,102) with a 4-year period after introduction of ticagrelor (2012-2015; n=7,348) respectively, in patients suffering from an ACS and undergoing a percutaneous coronary intervention (PCI). The adoption of ticagrelor was as high as >85% in patients with similar baseline characteristics as in the clopidogrel era. Therefore, a reliable comparison of clopidogrel and ticagrelor was possible without the risk of selection bias and with similar risk profile in both patients cohort regardless which P2Y₁₂ inhibitor was used. At 1-year follow-up the primary efficacy endpoint of death, myocardial infarction and ischemic stroke was similar between both drug regimens (5.6% vs. 6.0%) without any difference in safety concerns and bleeding (4.6% vs. 4.4%).

Despite being a centralized pre-post cohort analysis, there are several limitations such as restriction to first-time PCI patients, exclusion of patients requiring oral anticoagulation, missing data on stent thrombosis, missing

information for medication switch and data on preloading, which might explain the surprising findings in the „real-world“ setting by „exclusion“ of high-risk patients being associated with ischemic and bleeding events.

On the other hand, in a rapidly evolving field like interventional cardiology, results reported more than one decade ago with PCI in 64% using of bare-metal stents (BMS) in 42% first-generation drug-eluting stents (DES) in 19%, are likely to be outdated today, and even the analysis of Gro Thrane complies only partially with current standards.^{2,4}

With modern second-generation DES and third-generation thienopyridines, the rate of stent thrombosis and ischemic events are lower than with BMS and first-generation DES regardless of the used thienopyridine and duration of DAPT.⁵

Therefore, attention has shifted from stent thrombosis to downsides of DAPT, especially bleeding complications, which are in general higher with third-generation than second-generation thienopyridines.^{1,3,6}

The lack of any difference in bleeding events in the Danish registry analysis could be related to various causes, including a blanking period of 14 days after the index-procedure and the shift to clopidogrel in 13.6% of patients initially offered ticagrelor. Therefore procedure-related bleeding events, which are linked to the used thienopyridine, additional periprocedural anticoagulation (GPIIb/IIIa inhibitor in only 7.1% with ticagrelor, but in 43.3% with clopidogrel) and the preferred vascular access site (radial access in 10.4% in ticagrelor period and 5.4% in clopidogrel period), were not factored in by blanking the first 14 days after procedure, but are likely to explain the lower bleeding rate with ticagrelor despite a higher bleeding potential.

Addressing the clinical objective of reducing the risk of bleeding while increasing anti-ischemic effects requires dedicated and individualised approaches. There is evidence for shortened DAPT, for a de-escalation strategy, for radial access, and for vascular closure devices and gastric protection; all these measures are shown to reduce bleeding event rates without increasing the rate of ischemic events, whereas an unselected preloading with any antithrombotic agent was associated with higher rates of bleeding complications.^{6,7}

Moreover, in the complex scenario of ACS, the underlying athero-thrombotic risk is known to persist

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beyond the first year, even if successful and complete revascularization has been achieved at index-event.⁸ As demonstrated in the DAPT trial, half of athero-thrombotic events at long-term follow-up were not related to target lesion.⁹ Therefore, individual patient's overall multifactorial ischaemic risk should be taken into account to define the need for extending DAPT or a dual antithrombotic therapy (DAT) of low-dose factor-X inhibition with aspirin only.⁶⁻¹⁰

To better address both the short- and long-term risk of ischemic and bleeding events individually, several risk scores have been developed for personalized guidance. According to the results within the last decade, a „one-fits-all“ strategy is not recommended anymore; a statement that has not even been shattered by the Danish registry.⁴ Instead, the selective implementation of ticagrelor into a post-ACS scheme can be an important piece in the puzzle of personalized treatment as it is effective in the initial phase of thrombus activation particularly in high-risk patients; it appears also useful for long-term treatment to lower overall ischemic events in patients at low-bleeding risk. Nevertheless, with further evolution of modern antiplatelet and anticoagulation therapy, we believe that the last word has not been spoken yet and individualization of ischemic and bleeding risk may be instrumental to find a personalised treatment solution on the basis of current evidence from both RCT and recent registries. Future research should address these kind of multilevel individualized treatment strategies instead of „one-fits-all“ strategies to optimize the anti-ischemic effect without increasing bleeding rate.

Contributors

IA conceptualized the comment and wrote the first draft. CAN revised and improved the manuscript

Declaration of Interests

Authors have no interest to declare

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