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Personalised antiplatelet therapy: are we ready for prime time? Data from China

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Evolution of cardiovascular intervention in China

Since it was first introduced to China in the 1980s, percutaneous coronary intervention (PCI) has undergone a tremendous development[1,2]. In 2012, the total number of PCI cases increased to 388,836, compared with a total of 332,992 procedures performed in 2011. However, these cases were completed in 1,097 centres all over the country, and there has been an imbalance in the development of this technique. From 2007, the Ministry of Health (MOH) in China initiated several strategic programmes for improving the quality of this treatment. First, the National Interventional Cardiologist Training and Certification System was set up for personal accreditation. Eighty-four centres were assigned by the MOH as training centres, and 421 experienced cardiologists were authorised by the MOH to be the training mentors. A unified training programme was used with the requirement that the trainees must finish no fewer than 50 angiograms and 25 PCIs as the first operator supervised by the mentors in a 12-month training period. After having finished the training programme, the qualified trainees may take part in the National Interventional Cardiologist Certification Examination, and those who pass the exam may get certification from the MOH for a further application for a licence as an interventional cardiologist. So far, 1,904 trainees have gone through this system. Second, one national and 31 provincial PCI quality control centres were established in 2009 for consistent quality control and quality improvement. Regular on-site inspections as well as quality control discussion meetings were held periodically. At the end of each inspection, a performance report with quality of care suggestions were provided in real time to each hospital, and this report allowed hospitals to measure their own performance against a standard benchmark. Also, hospitals were encouraged to modify relevant aspects of the intervention therapy in an effort to improve their performance. Lastly, a national PCI databank was established in 2009, and the MOH issued the "Management and Techniques Specifications in Cardiovascular Interventions (2011 edition)" which outlines practice standards such that all PCI cases were required to be reported without delay through a website-based case reporting system. Since then, China has had data on PCI at a national level: the data will be analysed for quality control and quality improvement, and will be reported to the MOH as an important reference for policy making.

Generalisation and standardisation of PCI have always been pursued by interventional cardiologists in order to optimise this treatment. Most recently, with a better understanding of the genetic contributions to a patient's response to a specific therapy, personalised therapy has drawn lots of attention. With regard to personalised therapy in PCI, antiplatelet therapy has become the most promising research target.

Antiplatelet therapy research in China

Platelets are believed to play a key role in the pathogenesis of a coronary event, and antiplatelet therapy has been the fundamental treatment of coronary heart disease (CHD). A large number of clinical trials have been conducted to evaluate new antiplatelet regimens versus old ones, and this has promoted the frequent update of guidelines. China has always been passionate and active when it comes to participating in or conducting clinical trials evaluating antiplatelet therapies. The Second Chinese Cardiac Study (CCS-2) enrolled more than 45,000 Chinese acute myocardial infarction patients and compared dual antiplatelet therapy with clopidogrel and

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aspirin to mono antiplatelet therapy with aspirin in these patients[3], while the PLATO trial enrolled 416 Chinese acute coronary syndrome (ACS) patients and compared the efficacy/safety of the newer generation of the antiplatelet agent ticagrelor to clopidogrel, both on top of aspirin treatment. Data from Chinese patients enriched the evidence of antiplatelet therapy in ACS treatment. In this issue of EuroIntervention, the group of Ya-Ling Han published their original data on genetic determination of platelet response to

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clopidogrel and its impact on clinical outcomes in high-risk ACS patients receiving DES implantation and clopidogrel[4]. This study enrolled 1,016 high-risk Chinese ACS patients, of whom 9.5% were STEMI and 90.5% were NSTE-ACS subjects, with data on platelet function as well as on events in a one-year follow-up period. The results showed that homozygotes for the CYP2C19 loss of function (LOF) mutation were both an independent predictor of high post-treatment platelet reactivity (HTPR) (OR: 2.8, 95% CI: 1.70-7.23, p<0.001), and an independent predictor of adverse clinical outcomes during a one-year follow-up period (HR: 2.3, 95% CI: 1.40-4.97, p<0.001). Meanwhile, the post-procedure HTPR was also an independent predictor of adverse clinical outcome (HR: 2.9, 95% CI: 1.52-5.57, p<0.001). The findings of this study are of importance as, in the same study, it was demonstrated in high-risk Chinese ACS patients that the CYP2C19 LOF mutation was associated with poor platelet response to clopidogrel and, subsequently, was associated with poor clinical outcomes, while the previous studies had drawn controversial conclusions[5,6]. The results of this study will help us to understand further the impact of CYP2C19 polymorphism, as well as the difference of the impact of this polymorphism in different populations (previous studies had revealed there exists great variation regarding the frequency of the LOF allele[7]). Therefore, further studies need to be carried out to confirm the specific relationship between the genotype and phenotype variations and the clinical outcomes in Chinese patients.

Are we ready for personalised antiplatelet therapy NOW?

Though a series of studies has suggested that either genetic polymorphisms or the HTPR was significantly associated with atherothrombotic events, this might not be the right time to initiate personalised therapy depending simply on these limited data. As previously illustrated, the impact or the magnitude of the impact of genetic polymorphism may vary in different populations, and currently there is no consensus regarding the most appropriate method to quantify the magnitude of HTPR. Previous studies of treatment adjustment depending on platelet function monitoring failed to show any improvement in clinical outcome compared to the standard therapy without platelet function monitoring[8,9]. What then is the right way to optimise our antiplatelet therapy? Results of the POPULAR trial may give us some clues. In the POPULAR trial, different platelet function tests were compared head to head as regards their ability to predict thrombotic and bleeding events in ACS patients. One interesting finding was that the predictive power (ROC analysis) of these platelet test assays would be significantly increased (AUC 0.64 increased to 0.72, p=0.004) when adding multiple clinical and procedural factors, like lesion and stent characteristics, clopidogrel loading dose use, etc.[10], indicating that, at the current stage, if we want to optimise the antiplatelet treatment to a specific patient, we have to collect and integrate as many factors pertaining to this specific patient as we can, and only those treatment adjustments based on the "personalised" information would ultimately benefit our patients.

In summary, contemporary basic and clinical researches have evolved to embrace an increasingly sophisticated view of the mechanisms underlying antiplatelet response variability. The underlying mechanisms leading to poor response to antiplatelet agents have not been fully elucidated and are probably multifactorial. Treatment compliance, environmental and genetic factors are of importance; however, clinical factors such as obesity and diabetes mellitus are known to contribute to variable antiplatelet drug response. More evidence is expected to emerge in the future which will make things clearer.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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