Editorial

Individualized Antiplatelet Therapy: A Long Way to Go

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Antiplatelet therapy is the cornerstone for the management of patients with coronary artery disease. In the past two decades, the study on individualized antiplatelet therapy has never been more prosperous accompanied with the rapid growth of percutaneous coronary interventions (PCIs).[1]

Thrombosis and bleeding are the two sides of a coin. The fundamental idea of optimal antiplatelet therapy is to weight its pros and cons carefully, in order to maximize the benefit and minimize the potential risk simultaneously. According to this principle, tens of thousands studies have been launched and published and have changed the current guidelines and clinical practice. However, there are still many questions unsolved in this area.

The question that needs to be answered preferentially is how to identify thrombotic/bleeding risk precisely for every single individual. As we know, thrombosis and bleeding are both multifactorial disorders. Clinical characteristics, coronary anatomy, procedure related factors, platelet function, genotype, treatment compliance, social economic status, ethnicity, and mental condition, are all relevant to risk of thrombotic/bleeding events. Many independent predictors have been identified in different patient cohorts such as diabetes mellitus, renal insufficiency, acute coronary syndromes (ACSs), complex PCI, residual platelet reactivity, and cytochrome P450 2C19 loss-of-function alleles. Unfortunately, most of them were studied separately, which might always lead to over- or underestimate of global risks, and therefore seldom of them can be successfully served as a risk stratification parameter for the guidance of personnel tailored antiplatelet therapy. Recently, some scoring systems (DAPT, Precise DAPT, PARIS, etc.) were developed specially for decision-making on optimizing antiplatelet therapy.[2-4] However, all of them were derived from populations with inclusion/exclusion criteria but not "all-comers;" therefore, their accuracy and generalizability were questioned and need to be verified in real-world practice.

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The other important question on individualized antiplatelet therapy is how to treat a patient properly at a knowing baseline risk. During the past two decades, many optimizing antiplatelet regimens were tested. Two pivotal randomized studies, CURE and CREDO,[5,6] established the role of dual antiplatelet therapy (clopidogrel and aspirin) in preventing thrombotic events in patients with ACS and/or undergoing PCI. The concerns on late catchup and stent thrombosis after drug-eluting stent (DES) implantation sparked the arguments on prolonging duration of dual antiplatelet therapy.[7] The understanding of poor responsiveness to antiplatelet agents led to the explorations on platelet function/genotype-guided treatment,[8-10] as well as more intensive treatment strategies such as high maintenance dose clopidogrel, triple antiplatelet therapy with cilostazol on the top of dual antiplatelet therapy, and using more potent P2Y12 inhibitors, prasugrel and ticagrelor, which had proven superior to clopidogrel in high risk ACS patients, at a cost of increased bleeding risk.[11,12] On the other direction, subtraction on antiplatelet therapy in selected patients is tried in order to enhance safety and cost-effectiveness. Six-month dual antiplatelet therapy which is proven had same efficacy and safety compared with the standard 12-month dual antiplatelet therapy in patients who underwent new-generation DES implantation,[13] which was associated with lower risk of stent thrombosis compared to first-generation DES. De-escalation of antiplatelet therapy in stabilized patients, i.e., switching from dual antiplatelet therapy to single P2Y12 inhibitor or switching from potent P2Y12 inhibitors to clopidogrel,[14-17] is now under study. Based on the above explorations, benefits and risks of different antiplatelet regimens have been illustrated.

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However, the evidence on patients with specific risks, such as ≥75 years old, chronic kidney disease, diabetes, anemia, thrombocytopenia, high risk of gastrointestinal bleeding, and indication of oral anticoagulant agent, is still insufficient, because those patients were always excluded in pivotal trials and most of existed evidence is derived from retrospective or *post hoc* analysis.

Given the complexity of individual pathophysiology and responsiveness to antiplatelet agents, although a great many of clinical evidence has been accumulated and some of them are changing our practice, we are far from mastering the golden key to treat individual patient precisely. Several large-scale, randomized trials failed to demonstrate the clinical benefit of personnel tailored antiplatelet therapy, indicating that individual risk might not be well estimated.[8,9] To solve this problem, we have a long way to go. First, more comprehensive predictor model should be built to know the global risk of thrombosis and bleeding for a single individual. Considering the diversity of the real-world practice, a huge amount of high-quality data is needed to deduce an ideal model. Fortunately, rapid development on big data analysis and artificial intelligence (AI) technique will provide great help to this work. In the future, it is not hard to image that, with key information input, decision on individualized antiplatelet therapy will be made under the help of AI. Second, efficacy and safety of different antiplatelet regimens in patients at different risk profiles should further be studied, especially in all-comers and special patient subsets. Clinical studies will provide not only treatment-related evidence but also high-quality comprehensive data. The more data we have, the closer we get to the nature of individualized antiplatelet therapy. Third, attempts to find novel antiplatelet agents are still in progress. Therefore, efficacy and safety of some new antiplatelet agents, such as vicagrel, cangrelor, and platelet-activating factor inhibitor, should be evaluated in general and specific patient cohort.

The morbidity and mortality of cardiovascular disease (CVD) in China has been steadily increased for more than 10 years. According to the 2016 Chinese annual reports on CVD, there are nearly 290 million CVD patients in China, which are the leading cause of death. Given that arterial thrombotic complication is one of the most important causes of death, optimal antiplatelet therapy is an urgent need for Chinese CVD patients. Furthermore, an expert consensus has reported that East Asian patients were at comparable or lower risk of thrombotic events but greater risk of bleeding compared with Caucasian patients, the so-called "East Asian paradox,"[18] which called for more ethnic-specific evidence to optimizing antiplatelet therapy in clinical practice. However, during the past decade, high-quality clinical trials concerning in antiplatelet therapy in China are very limited. As pointed out in an interview published in Circulation, insufficient funding, inexperienced research team, too much clinical load, and lack of incentive mechanisms are main challenges in conducting clinical trials in China.[19] Fortunately, the situations are changing. With the rapid developments on clinical research teams, facilities, and environment, the evidence from China has been emerging.

Our team, growing together with other famous cardiac centers in China, has launched serial of clinical trials targeting on optimal antiplatelet therapy, under the support of the National Key Research and Development Project during the Twelfth and Thirteenth Five-year Plan. Most of our trials were focused on optimal durations of dual antiplatelet therapy and novel antiplatelet regimens on specific patient subset, such as patients with diabetes, chronic kidney disease, and poor responsiveness to clopidogrel.[20] Some of our findings have been adopted by domestic and European guidelines.[13,21] Furthermore, we are now investigating novel biomarkers, instruments, and indexes to find out the therapeutic window of antiplatelet therapy in Chinese patients. With great efforts of all participants, a nationwide antiplatelet cohort has been established which enrolled more than 20,000 CVD patients and all patients will be clinically followed up for 5 years. Based on this cohort study, we sought to find out the current antiplatelet status, clinical outcomes, and predictors of prognosis in Chinese CVD patients, and to establish thrombotic/bleeding scoring system suit for Chinese patients. We sincerely expect and believe that our work will provide valuable thoughts and evidences to individualized antiplatelet therapy, especially for Chinese CVD patients.

References

1. Zhu P, Gao Z, Tang XF, Xu JJ, Zhang Y, Gao LJ, *et al.* Impact of proton-pump inhibitors on the pharmacodynamic effect and clinical outcomes in patients receiving dual antiplatelet therapy after percutaneous coronary intervention: A Propensity score analysis. Chin Med J 2017;130:2899-905. doi: 10.4103/0366-6999.220304.
2. Yeh RW, Secemsky EA, Kereiakes DJ, Normand SL, Gershlick AH, Cohen DJ, *et al.* Development and validation of a prediction rule for benefit and harm of dual antiplatelet therapy beyond 1 year after percutaneous coronary intervention. JAMA 2016;315:1735-49. doi: 10.1001/jama.2016.3775.
3. Costa F, van Klaveren D, James S, Heg D, Räber L, Feres F, *et al.* Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: A pooled analysis of individual-patient datasets from clinical trials. Lancet 2017;389:1025-34. doi: 10.1016/S0140-6736(17)30397-5.
4. Baber U, Mehran R, Giustino G, Cohen DJ, Henry TD, Sartori S, *et al.* Coronary thrombosis and major bleeding after PCI with drug-eluting stents: Risk scores from PARIS. J Am Coll Cardiol 2016;67:2224-34. doi: 10.1016/j.jacc.2016.02.064.
5. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK, *et al.* Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med 2001;345:494-502. doi: 10.1056/NEJMoa010746.
6. Steinhubl SR, Berger PB, Mann JT 3rd, Fry ET, DeLago A, Wilmer C, *et al*. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: A randomized controlled trial. JAMA 2002;288:2411-20. doi: 10.1001/jama.288.19.2411.
7. Berger PB. Optimal duration of clopidogrel use after implantation of drug-eluting stents – Still in doubt. N Engl J Med 2010;362:1441-3. doi: 10.1056/NEJMe1002553.
8. Collet JP, Cuisset T, Rangé G, Cayla G, Elhadad S, Pouillot C, *et al.* Bedside monitoring to adjust antiplatelet therapy for coronary stenting. N Engl J Med 2012;367:2100-9. doi: 10.1056/NEJMoa1209979.

9. Price MJ, Berger PB, Teirstein PS, Tanguay JF, Angiolillo DJ, Spriggs D, *et al.* Standard- vs. high-dose clopidogrel based on platelet function testing after percutaneous coronary intervention: The GRAVITAS randomized trial. JAMA 2011;305:1097-105. doi: 10.1001/jama.2011.290.
10. Roberts JD, Wells GA, Le May MR, Labinaz M, Glover C, Froeschl M, *et al.* Point-of-care genetic testing for personalisation of antiplatelet treatment (RAPID GENE): A prospective, randomised, proof-of-concept trial. Lancet 2012;379:1705-11. doi: 10.1016/S0140-6736(12)60161-5.
11. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, *et al.* Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2009;361:1045-57. doi: 10.1056/NEJMoa0904327.
12. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, *et al.* Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007;357:2001-15. doi: 10.1056/NEJMoa0706482.
13. Han Y, Xu B, Xu K, Guan C, Jing Q, Zheng Q, *et al.* Six versus 12 months of dual antiplatelet therapy after implantation of biodegradable polymer sirolimus-eluting stent: Randomized substudy of the I-LOVE-IT 2 trial. Circ Cardiovasc Interv 2016;9:e003145. doi: 10.1161/CIRCINTERVENTIONS.115.003145.
14. Cuisset T, Deharo P, Quilici J, Johnson TW, Deffarges S, Bassez C, *et al.* Benefit of switching dual antiplatelet therapy after acute coronary syndrome: The TOPIC (timing of platelet inhibition after acute coronary syndrome) randomized study. Eur Heart J 2017;38:3070-8. doi: 10.1093/eurheartj/ehx175.
15. Sibbing D, Aradi D, Jacobshagen C, Gross L, Trenk D, Geisler T, *et al.* Guided de-escalation of antiplatelet treatment in patients with acute coronary syndrome undergoing percutaneous coronary intervention (TROPICAL-ACS): A randomised, open-label, multicentre trial. Lancet 2017;390:1747-57. doi: 10.1016/S0140-6736(17)32155-4.
16. Baber U, Dangas G, Cohen DJ, Gibson CM, Mehta SR, Angiolillo DJ, *et al.* Ticagrelor with aspirin or alone in high-risk patients after coronary intervention: Rationale and design of the TWILIGHT study. Am Heart J 2016;182:125-34. doi: 10.1016/j.ahj.2016.09.006.
17. He RX, Zhang L, Zhou TN, Yuan WJ, Liu YJ, Fu WX, *et al.* Safety and necessity of antiplatelet therapy on patients underwent endovascular aortic repair with both stanford type B aortic dissection and coronary heart disease. Chin Med J 2017;130:2321-5. doi: 10.4103/0366-6999.215330.
18. Levine GN, Jeong YH, Goto S, Anderson JL, Huo Y, Mega JL, *et al.* Expert consensus document: World Heart Federation expert consensus statement on antiplatelet therapy in East Asian patients with ACS or undergoing PCI. Nat Rev Cardiol 2014;11:597-606. doi: 10.1038/nrcardio.2014.104.
19. Han YL, Rutherford JD. Recent evolution of the treatment of coronary artery disease in China: A conversation with Ya-Ling Han, MD, PhD. Circulation 2017;136:2298-302. doi: 10.1161/CIRCULATIONAHA.117.032510.
20. Zhang L, Li Y, Yang BS, Li L, Wang XZ, Ge ML, *et al.* A multicenter, randomized, double-blind, and placebo-controlled study of the effects of tongxinluo capsules in acute coronary syndrome patients with high on-treatment platelet reactivity. Chin Med J 2018;131:508-15. doi: 10.4103/0366-6999.226064.
21. Han Y, Guo J, Zheng Y, Zang H, Su X, Wang Y, *et al.* Bivalirudin vs. heparin with or without tirofiban during primary percutaneous coronary intervention in acute myocardial infarction: The BRIGHT randomized clinical trial. JAMA 2015;313:1336-46. doi: 10.1001/jama.2015.2323.