Review Article

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The development of antiplatelet therapy after percutaneous coronary intervention

Abstract

Coronary artery disease is one of the common cardiovascular diseases and threatens our health. Percutaneous coronary intervention (PCI) is the main treatment for coronary artery disease. Bare-metal stents (BMS) and drug-eluting stents (DES) are popularly applied in clinical practice. With the development of clinic and technology, DES is widely used in coronary artery disease following antiplatelet therapy. Clinical guidelines require dual antiplatelet therapy (DAPT) after PCI in USA and Europe. It is effective to reduce the incident of stent thrombosis, myocardial infarction and major adverse cardiac. However, the risk of major adverse cardiac events and bleeding was increased by DAPT. Therefore, single antiplatelet therapy was induced in various clinical trials. We searched previous research from PubMed, Embase Web of Science published in English from Jan 1, 2000, to Nov 20, 2017 and screened clinical trials in the ClinicalTrials.gov. In this review, we discussed the efficacy of DAPT and prospective investigations of single antiplatelet therapy after PCI.

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Introduction

Coronary artery disease (CAD) is a common disease and has an impact in all over the word. With the development of life level and life style, the incident of morbidity and mortality largely increased.[1] Atherogenesis and the formation of thrombi are the main risk events. The application of percutaneous coronary intervention (PCI) released coronary artery disease and improved patients' quality of life. The mortality of acute coronary syndrome (ACS) was obviously reduced.[2] The stent style including bare-metal stents (BMS) and drug-eluting stents (DES) benefited many patients in clinic.[3] Antiplatelet therapy is standard treatment after PCI. Meanwhile, international guidelines and clinical practice recommend dual antiplatelet therapy (DAPT aspirin combination with P2Y12 inhibitors) after PCI.[4,5] Previous clinical application indicated that DES reduced major advent cardiac such as death, non-fatal myocardial infarction target lesion revascularization.[6] But the risk of stent thrombosis was increased, especially late stent thrombosis.[7] Therefore, in order to prevent stent thrombosis, prolonged antiplatelet therapy was recommended by clinical guidelines. Then DAPT combination of aspirin with P2Y12 inhibitors (clopidogrel, prasugrel, ticagrelor) used to reduce the risk of stent thrombosis and adverse cardiac outcomes. However, the optimal duration of DAPT after coronary drug-eluting stent implantation remains debated. It will elevate stent thrombosis if stopping DAPT too early. For the other side, delaying DAPT will increase patients' burden and reduce patients' compliance; what's more, the complication of bleeding will increase and it affects some surgeries. It is a challenge for clinician to balance the advantages and disadvantages.

Literature review

To discuss the development of antiplatelet therapy after percutaneous coronary intervention, we searched previous research from PubMed Embase Web of Science published in English from Jan 1, 2000, to Nov 20, 2017 and screened clinical trials in the ClinicalTrials.gov. The literature was searched with relative words such as "coronary artery disease(CAD)", "acute coronary syndrome(ACS)", "dual antiplatelet therapy", "DAPT", "single antiplatelet therapy", "stent thrombosis", "percutaneous coronary intervention(PCI)", "Bare-metal stents(BMS)", "drug eluting stents (DES)" and "P2Y12 inhibitors".

The key point to antiplatelet therapy after PCI

Patients with ACS often burden with diabetes, hyperlipidemia, hypertension and platelet activation; all these risk may cause thrombosis. PCI is an effective treatment for patients with ACS. No matter, with BMS or DES, it is possibly damaged vascular which will activate platelet activity and induce thrombosis. Therefore, it is meaningful to administer antiplatelet therapy after PCI. Nowadays, aspirin and clopidogrel are the main drug applied in antiplatelet therapy. Aspirin used to antiplatelet for a long time and it can inactivate cyclooxygenase (Cox) by combining with the activity of Cox-1, resulting in a decreased production of thromboxane A2(TXA2), induced to inhibit platelet aggregation. Clopidogrel is an ADP-receptor inhibitor, which widely used in the clinic. Before binding to the platelet P2Y12 ADP receptor, clopidogrel need two steps metabolic transformation. And clopidogrel inhibits GPIIb/IIIa activation to prevent thrombotic complications. To inhibit platelet reactivity and platelet aggregation effectively reverses ACS and prevents thrombotic. Thus, DAPT combination with aspirin and clopidogrel has become standard treatment in clinical practice.[4]

The efficacy of dual antiplatelet therapy

Aspirin combination with P2Y12 inhibitors is standard therapy for patients after PCI. Many patients benefit from DAPT. While the risk and the duration of DAPT is different in various patients. For patients with high risk of bleeding 3-6 months duration of DAPT was recommended for patients after PCI by European and USA guideline; for patients with stable coronary artery disease(SCAD)≥6-month duration of DAPT was recommended; for patients with ACS, more than 12-month duration of DAPT was recommended.[4,5,8] How to balance the abbreviated DAPT and prolonged DAPT carried out in numerous clinical trials. It is unclear to assess the efficacy of

prolonging DAPT. Several clinical trials were conducted to explore this problem. A randomised trial, ARCTIC-Interruption of 1259 eligible patients, indicated that patients stented with DES combined with DAPT beyond 1 year cannot benefit.[9] Other clinical trials including DES LATE enrolling 5045 patients[10] PRODIGY enrolling 1970 patients[11] OPTIDUAL[12] enrolling 1305 patients got similar results-no differences. The duration of dual antiplatelet therapy was 12 vs 36 months, 6 vs 24 months and 12 vs 48 months, respectively. While DAPT trial enrolling 9961 patients demonstrated that patients benefit from 30-month duration of dual antiplatelet therapy.[13] The risk of major adverse cardiac and cerebrovascular events reduced. In contrast to prolonged DAPT the abbreviated DAPT shown noninferiority in clinical research. The superiority of abbreviated DAPT was unclear. For example, ISAR-SAFE trial enrolling 4005 patients to compare the clinical outcome with the duration of clopidogrel therapy after DES for 6-month or 12-month.[14] This trial demonstrated that there was no significant difference between 6-month and 12-month in stent thrombosis, myocardial infarction and death. In order to shorten the duration of DAPT, BMS used more regularly than DES in elderly patients. But there was no research to detect the outcome for this strategy. Therefore, Olivier Varenne and his colleague performed SENIOR trial to explore the difference in two stent styles [6] SENIOR trial indicated that a short duration of DAPT combined with DES reduced myocardial infarction all-cause mortality, and ischemia-driven target lesion revascularization compared with BMS combination with similar duration of DAPT for elderly patients with PCI.

Continued DAPT may affect patients' quality of life or increase the risk of bleeding. In the present, there is no clinical trial to demonstrate this issue. The PARIS (patterns of non-adherence to antiplatelet regimens in stented patients) trial is a prospective observational study enrolling PCI patients to explore associations between cardiovascular risk and different modes of DAPT cessation after PCI.[15] The PARIS showed that DAPT cessation may increase the risk of cardiovascular risk. The reasons depend on different factors such as clinical circumstance, reason for the cessation mode of cessation and patient decision. Tullio Palmerini and his colleague performed a pairwise and Bayesian network meta-analysis to analyse the optimal duration of DAPT in many randomised trials.[16] They concluded that shorter DAPT lower all-cause mortality compared with longer DAPT and shorter DAPT reduced the risk of major bleeding but increased myocardial infarction and stent thrombosis; network meta-analysis shown that the risk of lower all-cause mortality and non-cardiac mortality observed in patients with DAPT for 6-month or shorter or for 1 year than patients treated over 1 year.

The event of bleeding by antiplatelet therapy

Bleeding was one of the main risks of DAPT. Aspirin blocks the synthesis of prostacyclin in the gastric mucosa, weakening the gastric mucosal barrier, doing harm to the gastric mucosa and even causes bleeding.[17] Although clopidogrel is not the main cause of ulcer formation it inhibits the release of vascular endothelial growth factor from platelets; this may impair the healing of the ulcer and convert the quiescent ulcers into hemorrhagic lesions to delay healing of the ulcer.[17,18] Therefore, combination aspirin with clopidogrel may be increased gastric mucosal damage, to extend its recovery time. Gastrointestinal bleeding is one of the major adverse events of antiplatelet therapy, accounting for about 50% of all bleeding after PCI. Studies have shown that the incidence of gastrointestinal ulcer

in patients taking long-term aspirin was 1-2%; for patients with ulcer, long-term use of aspirin can induce rebleeding in 15% of patients. Research indicated that clopidogrel alone caused gastrointestinal bleeding less likely than aspirin alone; aspirin combined with clopidogrel may increase the risk of gastrointestinal bleeding about 7-14 times. A case-control cohort study in the United States enrolled 1852 patients with dual antiplatelet therapy after PCI in coronary heart disease. Of these patients, the rate of gastrointestinal bleeding was 2.7%.[19]

Rational for single antiplatelet therapy

Accumulative evidence indicated that DAPT may increase the risk of gastrointestinal bleeding.[20] Of note, this inferiority may induce bleeding-related death. To explore whether single antiplatelet therapy could reduce the risk of bleeding, an open-label, multicentre, randomised, controlled trial was induced. This trial indicated that the application of clopidogrel alone reduced the risk of bleeding and the rate of thrombotic events compared with clopidogrel combined with aspirin in patients after PCI.[21] Although clopidogrel alone or aspirin alone achieved clinical outcome, some interesting was founded. For instance, aspirin resistance and clopidogrel resistance were observed in clinical practice.[22,23] Therefore, novel effective drugs are needed. Similar to clopidogrel, prasugrel and ticagrelor are oral P2Y12-receptor inhibitor to inhibit platelet activation and aggregation.[24] The difference is that prasugrel requires metabolic activation; but ticagrelor can be activated directly. Compared with clopidogrel, both of them have a faster onset of action.[25] Clinical efficacy and outcome were improved by use of prasugrel and ticagrelor. The platelet signals of ADP–P2Y12-dependent and thromboxane A2-dependent were effectively inhibited by prasugrel and ticagrelor, which was superior to aspirin. It is possible that these P2Y12-receptor inhibitors use as single antiplatelet therapy for patients after PCI.

In addition, single antiplatelet therapy has applied in secondary prevention. For secondary prevention, SOCRATES trial was conducted to test the efficacy of ticagrelor versus aspirin.[26] The results showed that no difference was observed among the risk of death, myocardial infarction, stroke and the rate of major bleeding. The reason may be the following up was shorter (90 days), and the effect of ticagrelor was not superior to aspirin. Therefore, another longer follow-up study of single antiplatelet therapy designing for secondary prevention should be performed.

Ongoing trials of single antiplatelet therapy

There are three ongoing trials of P2Y12-receptor monotherapy after PCI. GLOBAL LEADERS trial is the largest ongoing trial that has enrolled 16001 patients.[27,28] This study is conducted to assess the efficacy between long-term ticagrelor monotherapy and standard DAPT after biolimus-eluting stent implantation. STOPDAPT-2 trial is a phase IV study that will enroll 3000 patients who underwent PCI.[29] This trial will evaluate the effect of 1-month DAPT followed by 59-month clopidogrel compared with 1-month DAPT followed by 11-month aspirin combined with clopidogrel and followed by 48-month aspirin. TWILIGHT trial is a double blind, multicentre, phase IV study[30] this trial intend to enroll 9000 high-risk patients to explore the efficacy of ticagrelor (90mg twice daily) combined with placebo compared with ticagrelor (90mg twice daily) combined with aspirin (81 mg). For patients with SCAD or ACS these ongoing trials may provide evidence to support single antiplatelet therapy.

Cardiac rehabilitation after PCI

Cardiac rehabilitation has been applied to several cardiovascular diseases such as myocardial infarction[31] percutaneous coronary intervention and coronary artery bypass graft surgery.[32] National guideline also recommends cardiac rehabilitation to patients with those diseases.[33] Previous research showed that cardiac rehabilitation could reduce the morbidity and mortality in cardiovascular disease.[34] Cardiac rehabilitation is an important component after PCI. However, cardiac rehabilitation services are underused. Some studies were investigated to explore the reasons. Brown et al.[32] extracted data from the American Heart Association's Get With The Guidelines program indicated that patients with comorbidity non–ST-segment elevation myocardial infarction, older age would have less chance to receive cardiac rehabilitation services.[32] Aragam et al.[35] performed a study enrolling 1432399 patients at 1310 participating hospitals between 2009 and 2012 in the United State, which demonstrated only 60% patients after PCI received cardiac rehabilitation Aragam et al.[35] Found that the rate of cardiac rehabilitation referral was associated with hospital characteristics, patient factors and insurance status; and the relevance of three factors gradually declined. All these factors could be overcome. Moreover, patients could benefit from cardiac rehabilitation services, it was imperative to increase the rate of referral to cardiac rehabilitation.

Discussion and future directions

Dual antiplatelet therapy with the combination of aspirin with P2Y12-receptor inhibitors has become standard care for patients after PCI. To some extent, DAPT improved clinical efficacy. However, the risk of major adverse cardiac events, bleeding and death still existed during DAPT. Many multicenter prospective studies have paid attention to the duration of DAPT clinical setting or other characteristics. But they just focused on one point or two points. To improve clinical outcome and efficacy, the duration of DAPT, clinical setting, patients' characteristics, time of randomization, primary end point major safety end point, follow up duration should be taken into consideration. It is better to uniform these factors. To reduce the risk of adverse cardiac events and bleeding, single antiplatelet therapy is another good choice. Moreover, secondary prevention with single antiplatelet therapy is being carried out by three ongoing trials. These prospective investigations will contribute to figure out the optimal treatment of antiplatelet therapy after PCI. Cardiac rehabilitation not only reduced the morbidity and mortality of cardiovascular disease but also improved the quality of life. And cardiac rehabilitation played a vital role in the secondary prevention of cardiovascular disease. Therefore, antiplatelet therapy combined with cardiac rehabilitation services might benefit patients. Further investigations are needed to prove the effect of antiplatelet therapy in combination with cardiac rehabilitation services.

Conclusion

Although DAPT with a combination of aspirin and clopidogrel is the main treatment for patients after percutaneous coronary intervention, the risk of bleeding, stent thrombosis, myocardial infarction and major adverse cardiac still exists. Most importantly, the optimal duration of DAPT is debated. With the advancement of stent technology and the development of antiplatelet drugs an improved understanding of the role of single antiplatelet therapy has important clinical implications. Cardiac rehabilitation services may be a good choice to improve clinical outcome and quality of life.

Acknowledgements

Conflict of interest

The author declares no conflict of interest.

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