Journal of Cardiology xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Journal of Cardiology

journal homepage: www.elsevier.com/locate/jjcc

Review

Individualized antiplatelet therapy after drug-eluting stent deployment: Implication of clinical trials of different durations of dual antiplatelet therapy

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ARTICLE INFO

Article history:
Received 6 June 2017
Accepted 9 June 2017
Available online xxx

Keywords:
Dual antiplatelet therapy
Drug-eluting stent
Bleeding complication
Ischemic event

ABSTRACT

At present, there is consensus that prolonged dual antiplatelet therapy (DAPT) is effective to reduce cardiovascular events at the expense of bleeding complication events. A causal relationship of prolonged DAPT with an increase in mortality remains debatable, however, it appears to be obvious that bleeding complications are associated with an increase in cardiac events. Thus, individualized optimal DAPT duration balancing the risk and benefit of DAPT should be applied. In addition, strategy to minimize bleeding complications is highly recommended. Several risk scores have been reported to discriminate the risk and benefits of DAPT. However, in general, bleeding risk and event risk are correlated with each other, thus predictability of these scores is limited to moderate. Therefore, interpretation of previous trials is important to overcome the shortcome in outcomes. In this review, we provide an overview of DAPT trials and clarify the shortfalls to consider in Japan. Finally, possible future trends with reference to the results of recent clinical trials will be presented.

Contents

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http://dx.doi.org/10.1016/j.jjcc.2017.06.003
0914-5087/

Introduction

Physicians and researchers are generally undecided about the optimal antiplatelet therapy after drug-eluting stent (DES) placement, although the updated American College of Cardiology/American Heart Association guideline has thrown some light on this issue. The updated guideline suggests that the optimal treatment period should be determined on the basis of the following points: whether the patient has acute coronary syndrome, whether the patient is at high risk of bleeding complications, and whether the patient is at high risk of thrombotic complications [1]. Thus, individualization of dual antiplatelet therapy (DAPT) duration after DES deployment should be the right direction to go, however, this updated guideline fails to explain how to decide the duration of treatment in individual patients. The treatment strategy should be decided considering a variety of investigations previously reported. Although, interpretation of these trials is not easy due to inhomogeneous design of trials and inconsistent outcomes [2–9]. Many meta-analyses have been conducted, but standardization of optimal duration of DAPT remains to be determined. Thus, this article provides an overview of available results of recent clinical trials and focus on the future direction in Japan.

Changes in the position and duration of DAPT

DAPT was established as a standard treatment for the prevention of stent thrombosis in the bare metal stent (BMS) era [10]. At that time, 3 months of DAPT followed by a single antiplatelet agent was considered to be sufficient for the prevention of stent thrombosis, because endothelialization which directly linked to the reduction of the risk of stent thrombosis was expected to develop within 3 months after BMS deployment. After DAPT overcame the problem of stent thrombosis, the primary concern of physicians at that time was how to reduce restenosis, which frequently occurred from 6 months after BMS implantation. With the advent of DES, very late stent thrombosis (VLST) emerged as an important issue and long-term DAPT became the preferred therapy to prevent VLST. This is because the risk of VLST seemed to increase over time with first-generation DES. When safer second-generation DES became available, physicians started to consider the possibility of shortening the duration of DAPT. A clinical trial performed in patients with a high risk of stent thrombosis (including those with acute myocardial infarction) demonstrated the superior safety of 2nd generation DES over BMS [11]. This was followed by a number of non inferiority trials investigating the net clinical benefits of short-term DAPT compared with long-term DAPT [3–5,8,9]. In fact, these trials generally showed non inferiority of the short DAPT regimens. While a new trend to adopt DAPT regimens with a shorter duration was initially expected, this did not occur because of the results of the DAPT trial, which revealed the efficacy of long-term DAPT for reducing cardiovascular events [7]. The subsequent PEGASUS trial also showed efficacy of long-term DAPT. The PEGASUS trial was conducted in patients with old myocardial infarction [without percutaneous coronary intervention (PCI)] and showed that DAPT decreases ischemic events [12]. Taken together, expectations about the purpose of DAPT slowly changed from the prevention of stent thrombosis to long-term prevention of ischemic events.

Concern about bleeding complications

To improve the outcomes of PCI in the setting of acute coronary syndrome, potent antiplatelet drugs such as prasugrel and ticagrelor were developed. Both TRITON-TIMI 38 and PLATO trials using these potent platelet P2Y12 antagonists demonstrated a decrease in thrombotic events at the expense of excess bleeding complications [13,14]. Subsequently, bleeding complications during DAPT were frequently reported [15–17]. Table 1 summarizes the potential problems and characteristics of bleeding complications during DAPT. It was reported that even minor bleeding, such as Bleeding Academic Research Council 1 and 2 bleeding (events that previously received little attention), is correlated with cardiovascular (CV) events [15]. On the other hand, the causal relationship between bleeding complications and subsequent increase in the all-cause mortality which is attributable to non-cardiac mortality remains controversial. In fact, recent meta-analyses demonstrated inconsistent outcomes regarding this relationship [16,17]. However, it seems to be difficult to ignore the impact of bleeding complications. Currently the risk evaluation and management of bleeding complications are important determinants for the optimal DAPT duration.

Table 1
Characteristics and potential problem of bleeding complications during DAPT.

1. DAPT is associated with higher bleeding complication risk
2. Risk of bleeding complications is continuous
3. Bleeding complications result in the increase of cardiac event risk
4. Minor bleeding such as BARC 1,2 may correlate with cardiac event
5. Approximately 60% of the cause of bleeding episode is gastrointestinal related
6. Bleeding complication has causal relationship with subsequent increase of mortality?

DAPT, dual antiplatelet therapy; BARC, Bleeding Academic Research Council.

Points of care for the prevention of bleeding complications

Table 2 depicts the treatment strategy with a possibility to avoid any bleeding episode at the time of PCI and during follow-up. Recently, many trials demonstrated that PCI via radial approach decreased the risk of bleeding complications and CV events compared with PCI via femoral approach [18,19]. Thus, it is obvious that PCI treatment by radial approach is ideal especially in patients with high risk of bleeding. The timing of platelet P2Y12 antagonist loading is also an important factor to prevent bleeding complications. The ACCOST trial demonstrated that pre-hospital half-dose loading of prasugrel did not reduce the CV events but increased the bleeding complication in non-ST elevation myocardial infarction (NSTEMI) patients [20]. On the other hand, the ATLANTIC trial showed that pre-hospital ticagrelor in STEMI patients was not associated with the improvement of primary end point (status of myocardial perfusion) but improved the first 24 hours' outcomes after PCI [21]. In this study, the median time difference between loading and coronary angiogram was limited to 31 min. Thus, it seems to be reasonable to consider that the loading once after confirmation of coronary anatomy is justified in NSTEMI patients, and on the other hand more rapid antiplatelet reaction may be mandatory in STEMI patients. The importance of prophylactic use of proton pump inhibitors (PPIs) after DES deployment may be

Table 2
Treatment strategy to prevent and avoid bleeding complications.

1. Prophylactic PPI therapy
2. The use of radial approach for PCI
3. Consider the optimal timing of P2Y12 loading
4. Adjust the dose of anticoagulant, and select the anticoagulant with lower risk of bleeding at the time of PCI
5. Select the treatment strategy that does not require long-term DAPT
6. Shorten DAPT duration in patients with high risk of bleeding
7. Early suspension of ASA may be appropriate
8. GI examination may be recommended prior to stenting

PPI, proton pump inhibitor; PCI, percutaneous coronary intervention; DAPT, dual antiplatelet therapy; ASA, aspirin; GI, gastrointestinal.

Please cite this article in press as: Nakamura M, et al. Individualized antiplatelet therapy after drug-eluting stent deployment: Implication of clinical trials of different durations of dual antiplatelet therapy. J Cardiol (2017), http://dx.doi.org/10.1016/j.jjcc.2017.06.003