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Dual Antiplatelet Therapy Duration: A Review of Current Available Evidence

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ABSTRACT

Purpose: Multiple regimens of antiplatelet and anticoagulation therapy have been used in the past in patients undergoing percutaneous coronary intervention (PCI). Later trials of PCI stenting demonstrated the efficacy of dual-antiplatelet therapy (DAPT) in reducing stent- and non–stent-related thrombotic events in this specific population. Nonetheless, the required duration of DAPT has not yet been elucidated. In this article we sought to identify various randomized clinical trials (RCTs), pooled analyses, meta-analyses, and data pertaining to the optimal duration of DAPT and attempt some recommendations based on patients' clinical and procedural profiles.

Methods: We performed an extensive search using MEDLINE, Scopus, Cochrane Library, and Internet sources for abstracts, manuscripts, and conference reports without any language or date restrictions. In our review we included all available evidence from RCTs, meta-analyses, observational studies, and abstracts pertaining to our topic. Search results that were deemed irrelevant or that would not serve the goal or topic of our review were excluded.

Results: Our search yielded 10 RCTs directly comparing different durations of DAPT, 3 meta-analyses amassing the evidence resulting from randomized data, and numerous observational studies that served the aim of our review. The observational studies included in the manuscript are directly related to instances in which RCTs could not be performed or introduce important concepts related to the duration of DAPT.

Implications: There is no conclusive evidence that determines the mandatory DAPT duration after PCI. In addition, there are distinct patient populations that need specific treatment regimens, such as diabetic patients or those on long-term oral anticoagulation. Therefore, clinical judgement and meticulous examination of all pertaining risk factors are required for each individual. These factors include those related to a patient's characteristics, treatment procedures, lesion complexity, and stent type. Currently ongoing studies are anticipated to further elucidate and integrate our understanding with regard to DAPT. (*Clin Ther*. 2016;▮:▮▮▮–▮▮▮) © 2016 Elsevier HS Journals, Inc. All rights reserved.

Key words: dual antiplatelet therapy, DAPT duration, percutaneous coronary intervention.

INTRODUCTION

Since its inception, percutaneous coronary intervention (PCI) accompanied by stent implantation has always been followed by various types of platelet inhibition. The importance of platelet inhibition was shown early in studies in which patients treated with a combination of aspirin and dipyridamole before PCI had lower rates of evidenced thrombi after successful percutaneous transluminal coronary angioplasty.[1] Different regimens have been used to reduce increased platelet and endothelial thrombogenicity after PCI, including aspirin, warfarin, dipyridamole, and ticlopidine.[2–5] In 2001, the CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) study[6] found that the addition of clopidogrel to a regimen of aspirin resulted in a 2% reduction in the risks for cardiovascular events, including myocardial infarction (MI) and stroke, in patients with acute coronary syndromes (ACSs), although with an associated increase (1%) in major bleeding events. The CREDO

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(Clopidogrel for the Reduction of Events during Observation) trial[7] found that prolonged therapy with clopidogrel after PCI also significantly reduced the risk for death, MI, and stroke at 1 year after randomization. Later on, the Percutaneous Coronary Interventions Clopidogrel in Unstable Angina to Prevent Recurrent Events (PCI-CURE) substudy[6,8] demonstrated that the initiation of clopidogrel before PCI and its continuation for a mean of 8 months after PCI with stent implantation, along with aspirin, would confer a considerable mortality benefit in patients receiving a stent compared with those treated solely with aspirin. This finding was confirmed by later studies.[9] Therefore, the combined use of 2 antiplatelet medications has been established as the standard of care in patients undergoing PCI.[10]

While DAPT has been shown to protect against ischemic events, this benefit is accompanied by an increased risk for bleeding complications. Thus, the need for an ideal duration of DAPT in those patients is an important consideration for treating physicians. Multiple studies have been conducted in an effort to elucidate this complex question.[11–22] The development of new stent platforms, new PCI techniques, and new pharmacologic agents has perplexed the situation even more.[23] To date, there has been no clear answer as to what should be the recommended duration of DAPT. Safety concerns regarding prolonged-duration DAPT were originally expressed in the CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance) study.[9] In this study, although DAPT had no effect in ischemic outcomes in patients with stable coronary artery disease (CAD), it was associated with a significant increase in moderate bleeding and a numeric but nonsignificant increase in severe/fatal bleeding events.

Rather, an individualized approach is needed when considering the total duration of DAPT therapy. In this article, we aimed to review the current literature available in a systematic way and to provide helpful direction regarding this important but still controversial topic.

MATERIALS AND METHODS

We searched MEDLINE, Scopus, Cochrane Library, and Internet sources for abstracts, manuscripts, and conference reports without any language or date restrictions. To meet the goals of our review, we included randomized clinical trials (RCTs), pooled analyses, meta-analyses, and observational studies pertinent to the topic of our review. The following terms have been used alone or in combination: *dual antiplatelet therapy, drug-eluting stent, clopidogrel, aspirin, randomized clinical trial,* and *percutaneous coronary intervention*. Prespecified inclusion criteria were: (1) comparison between DAPT (aspirin plus a thienopyridine) versus aspirin alone, and (2) PCI with drug-eluting stent (DES) implantation. Prespecified exclusion criteria were: (1) duplicated data, and (2) ongoing trials without final results.

RESULTS

Current Randomized Data on DAPT Duration

A total of 10 RCTs have been conducted to date pertaining to the duration of antiplatelet therapy after PCI stenting during the acute (ST-elevation MI) or nonacute (non–ST-elevation acute coronary syndromes [NSTEACS]-stable angina) setting.[11–21] Of note, all of these trials used clopidogrel as the additional antiplatelet factor, and no data on the newer agents (ie, prasugrel and ticagrelor) were available. In broad terms, 2 categories of trials exist: (1) those that have tested the continuation of DAPT for >12 months, and (2) those that have tested a shorter course of therapy of <12 months.

Trials Comparing a 3- to 6-Month versus a 12-Month Regimen

The majority of trials have focused their interest in reducing the duration of DAPT therapy to <12 months (12 months is the duration recommended in current guidelines)[24,25], given the latest advances in stents; second-generation DESs; and, more recently, bioabsorbable scaffolds and drug platforms. The EXCELLENT (Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting) trial[11] was the first trial that aimed to provide answers on this topic. Overall, it enrolled 1443 patients and compared a 12-month versus a 6-month course of DAPT in both stable (49%) and ACS (51%) patients receiving either an everolimus or sirolimus DES. The general characteristics of this study population, as well as for the rest of the studies included in the present review, are available in Table I. The primary outcome was defined as target vessel failure, including a composite of cardiac death, MI, or target vessel revascularization