Meta-Analysis of Randomized Clinical Trials Comparing Short-Term Versus Long-Term Dual Antiplatelet Therapy Following Drug-Eluting Stents

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Current guidelines recommend 12 months of dual antiplatelet therapy (DAPT) after drug-eluting stent (DES) implantation in the absence of increased bleeding risk. Studies have suggested that early discontinuation of DAPT can result in an increased risk of stent thrombosis. However, given the potential for major bleeding, the optimal duration of DAPT after DES implantation remains uncertain. We searched PubMed, EMBASE, Scopus, and ClinicalTrials.gov databases from inception until October 2013 for randomized controlled trials that compared shorter versus longer DAPT duration after DES implantation. Four randomized controlled trials were included. A total of 4,081 patients received DAPT for 3 to 6 months, and 4,076 patients were treated with DAPT for 12 to 24 months. Oral DAPT consisted of aspirin and clopidogrel. There was no significant difference in the rate of the composite outcome of cardiac death or myocardial infarction between the short (3.3%) and prolonged (3.0%) DAPT groups (odds ratio 1.11, 95% confidence interval 0.87 to 1.43, $p = 0.41$). A landmark analysis performed at the time of discontinuation of DAPT in the short DAPT group demonstrated a nonsignificant higher rate of stent thrombosis in patients treated with a short course of DAPT (0.35% vs 0.20%, $p = 0.22$). Major bleeding was significantly higher in the group of patients treated with prolonged DAPT (0.29% vs 0.71%, $p = 0.01$). In conclusion, prolonged DAPT compared with short-term treatment is associated with increased major bleeding but is not associated with a decrease in the composite rates of death or myocardial infarction. Published by Elsevier Inc. (Am J Cardiol 2014;114:236−242)

Polymer-coated stents that elute antiproliferative agents, commonly referred to as drug-eluting stents (DES), reduce target lesion restenosis compared with bare-metal stents.[1−4] On the basis of the first-generation DES clinical trial designs, dual antiplatelet therapy (DAPT) was initially recommended for 3 months after sirolimus-eluting stent and 6 months after paclitaxel-eluting stent implantation. Post-marketing experiences, however, demonstrated that early discontinuation of DAPT was associated with stent thrombosis (ST) after DES implantation.[5] Most of these thrombotic events tended to occur in the first 6 to 12 months after DES implantation and less so after the first year.[6−8] On the basis of these observations, the American College of Cardiology Foundation/American Heart Association/Society for Cardiovascular Angiography and Interventions guidelines for percutaneous coronary intervention recommend 12 months of DAPT after DES implantation in the absence of increased bleeding risk.[9] Recently, however, several reports have suggested an increased rate of bleeding events with prolonged compared with short DAPT but no significant difference in ischemic outcome.[10−19] Given the small number of events after discontinuation of the second antiplatelet agent in some of the individual studies, these studies were underpowered to detect a significant difference in individual ischemic events. Furthermore, some of these studies were observational in nature and, thus, are subject to selection bias. Therefore, we performed a meta-analysis of randomized controlled trials (RCTs) comparing short versus prolonged DAPT after DES implantation.

Methods

Two investigators (GE and AB) independently and in duplicate searched PubMed, EMBASE, Scopus, and ClinicalTrials.gov databases from inception until the end of October 2013 to identify RCTs comparing short DAPT (<6 months) to prolonged therapy (≥12 months) after DES implantation for cardiovascular outcomes and bleeding events. Search keywords were "dual antiplatelet therapy," "drug-eluting stents," "Aspirin," and "Clopidogrel." We also reviewed previous meta-analyses and the references of the selected studies. We did not set any search limitations by publication dates or language. We selected only those reports of RCTs examining various durations of DAPT after DES implantation. We excluded trials that exclusively enrolled patients treated with bare-metal stents and studies comparing standard 12-month DAPT with longer durations of DAPT.

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See page 241 for disclosure information.

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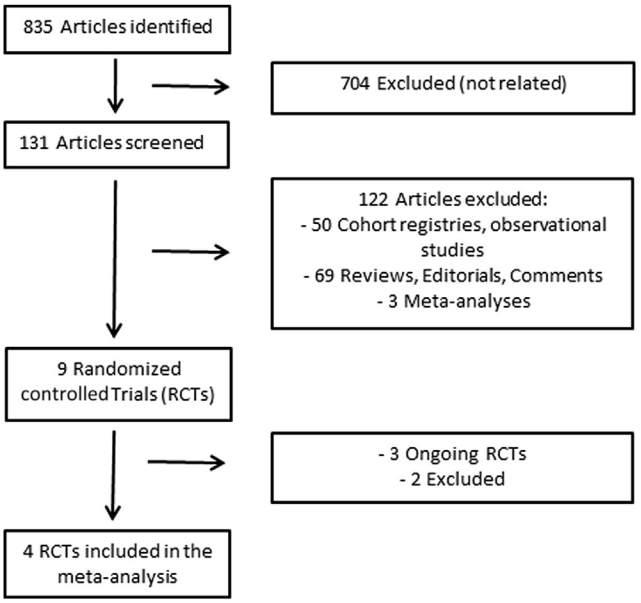

Figure 1. Algorithm of the literature search for studies included in the meta-analysis.

The primary outcome of this analysis was the composite end point of cardiac death or myocardial infarction (MI). We also evaluated the rates of the individual components of the primary outcome, and the rates of definite or probable ST, according to the Academic Research Consortium, target vessel revascularization, stroke, and major bleeding. Major bleeding was defined according to the definition used in each trial. Three trials defined major bleeding using the Thrombolysis in Myocardial Infarction criteria[12,14,16] and 1 trial used the Global Use of Strategies to Open Occluded Coronary Arteries criteria.[18] We performed a landmark analysis[20] at the time of discontinuation of DAPT in the short DAPT group comparing the rates of the composite end point of all-cause death or MI and the rates of definite or probable ST that occurred in follow-up for those patients who were free of events up until this landmark point. For this landmark analysis, patients were included in the denominator if they were free of clinical events as defined by the primary end point for each of the individual studies.

The statistical analysis was done in line with recommendations from the Cochrane Collaboration and the Preferred Reporting Items for Systematic reviews and Meta-analyses guidelines using Review Manager (RevMan), version 5.1.7 (Nordic Cochrane Centre, The Cochrane Collaboration, 2012, Copenhagen, Denmark). Heterogeneity was assessed using the I^2 statistic, defined as the proportion of total variation observed among the trials attributable to differences among trials rather than sampling error (chance) with values $<25\%$ considered as low and $>75\%$ as high.[21] Analysis was performed on an intention-to-treat basis. We performed fixed-effects analysis when I^2 was up to 25% and p value at least 0.05, otherwise we used random effects. Publication bias was estimated visually by funnel plots and/or using Begg's test and the weighted regression test of Egger.[22]

Results

As shown in Figure 1, 6 RCTs fit our primary selection criteria. We subsequently excluded 2 trials; one compared 12 versus 24 months of DAPT[11] and the second study randomized patients free of major adverse cardiovascular events and major bleeding after 12 months of DAPT to receive aspirin monotherapy or an additional 24 months of DAPT.[19] After exclusion, a total of 8,157 patients from 4 RCTs were examined. Of these, 4,081 patients were randomized to receive short-term DAPT and 4,076 to be treated with a prolonged course of DAPT. Table 1 depicts the design of the included trials. Randomization took place at the time of percutaneous coronary intervention in 3 trials[12,14,18] and 1 month after percutaneous coronary intervention in the fourth trial.[16] In the latter, cardiac events that occurred within 1 month of the index procedure were excluded. Oral DAPT consisted entirely of aspirin and clopidogrel. DAPT in the "experimental arm" consisted of a short course ranging from 3 to 6 months, whereas prolonged therapy varied from 12 to 24 months. In our analysis, the mean duration of DAPT was 4 months in the short-course therapy arm and 14 months in the standard or prolonged therapy arm. Follow-up duration was 12 months in 3 trials[12,14,18] and 24 months in the fourth trial.[16] Table 2 depicts the clinical characteristics of the patients and the procedural details in the 2 groups.

The composite outcome occurred in 136 patients (3.3%) randomized to short DAPT duration and in 123 (3.0%) of those randomized to prolonged therapy. As seen in Figure 2 and Table 3, there was no significant difference in the combined end point of cardiac death or MI between the 2 groups (odds ratio 1.11, 95% confidence interval 0.87 to 1.43, $p = 0.41$). There were significantly fewer bleeding events in the group of patients randomized to shorter DAPT compared with prolonged DAPT (0.29% vs 0.71%, $p = 0.01$). The odds of major bleeding in the shorter DAPT was 59% less than in the prolonged DAPT (odds ratio 0.41, 95% confidence interval 0.21 to 0.81; Figure 3). ST was numerically higher in the group of patients assigned to a short duration of DAPT, although this difference was not statistically significant (0.76% vs 0.59%, $p = 0.35$). We performed a landmark analysis for the composite outcome of all-cause death or MI and for the end point of ST beginning at the time of discontinuation of clopidogrel in the short-term therapy group. Only 3 trials reported on the incidence of the combined outcome all-cause death or MI during this period of time. Among patients who survived without clinical events to that landmark point, there was no significant difference in the rate of death or MI between the 2 groups (2.8% vs 2.6%, $p = 0.62$; Figure 4). There was a nonsignificant higher rate of ST in patients who remained on aspirin monotherapy compared with those who stayed on DAPT (0.35% vs 0.2%, $p = 0.22$; Figure 5).

Discussion

Our meta-analysis is the largest analysis comparing short versus prolonged DAPT after DES implantation, exclusively examining patients undergoing stent placement with a DES and selectively including all of the reported RCTs that have examined outcomes with a short course of