A prospective, randomized, open-label trial of 6-month versus 12-month dual antiplatelet therapy after drug-eluting stent implantation in ST-elevation myocardial infarction: Rationale and design of the "DAPT-STEMI trial"

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Background The optimal duration of dual antiplatelet therapy (DAPT) after percutaneous coronary intervention with second-generation drug eluting stents (DESs) is unclear. Because prolonged DAPT is associated with higher bleeding risk and health care costs, establishing optimal DAPT duration is of paramount importance. No other randomized controlled trials have evaluated the safety of shorter DAPT duration in ST-elevation myocardial infarction (STEMI) patients treated with second-generation DESs and latest P2Y12 platelet receptor inhibitors.

Hypothesis Six months of DAPT after Resolute Integrity stent implantation in STEMI patients is not inferior to 12 months of DAPT in clinical outcomes.

Study design The Dual Antiplatelet Therapy After Drug-Eluting Stent Implantation In ST-elevation Myocardial Infarction (DAPT-STEMI) trial is a randomized, multicenter, international, open-label trial designed to examine the safety (noninferiority) of 6-month DAPT after Resolute Integrity stent implantation in STEMI patients compared with 12-month DAPT. Event-free patients on DAPT at 6month will be randomized (1:1 fashion) between single (aspirin only) versus DAPT for an additional 6 months and followed until 2 years after primary percutaneous coronary intervention. The primary end point is a patient-oriented composite endpoint of all-cause mortality, any myocardial infarction, any revascularization, stroke, and major bleeding (net adverse clinical events [NACE]) at 18 months after randomization. To achieve a power of 85% for a noninferiority limit of 1.66, a total of 1100 enrolled patients are required.

Summary The DAPT-STEMI trial aims to assess in STEMI patients treated with second-generation DESs whether discontinuation of DAPT after 6 months of event-free survival is noninferior to routine 12-month DAPT. (Am Heart J 2017;188:11-17.)

The optimal duration of dual antiplatelet therapy (DAPT) after percutaneous coronary intervention (PCI) with second-generation drug eluting stents (DESs) is unclear.[1-3] Because prolonged DAPT is associated with higher bleeding risk and health care costs,[4] establishing optimal DAPT duration is of paramount importance. No other randomized controlled trials have evaluated the safety of shorter DAPT duration in ST-elevation myocardial infarction (STEMI) patients treated with second-generation DESs and latest P2Y12 platelet receptor inhibitors. Therefore, we have designed a prospective, randomized, open-label trial of 6 months versus 12 months of Dual Antiplatelet Therapy After Drug-Eluting Stent Implantation In ST-elevation Myocardial Infarction: the "DAPT-STEMI" trial to evaluate whether 6 months of DAPT after Resolute Integrity stent implantation in STEMI patients is not inferior to 12 months of DAPT in clinical outcomes.

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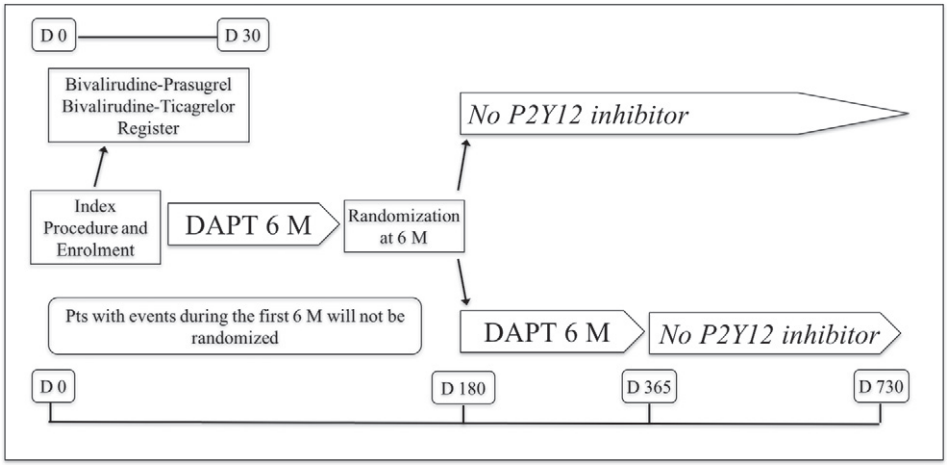
Figure 1



DAPT= dual antiplatelet therapy, M= months, Pts= patients

Study flowchart.

Study design

The DAPT-STEMI trial is a prospective, randomized, multicenter, international open-label trial testing the hypothesis that 6 months of DAPT after second-generation DES implantation in the setting of primary PCI for STEMI is not inferior to 12 months of DAPT (noninferiority hypothesis).

The trial will also incorporate 2 prospective registries studying:

1. the clinical outcomes after primary PCI with the Resolute Integrity (Medtronic, Santa Rosa, CA) stent at 30 days and 6 months (Resolute Integrity in STEMI Prospective Registry)
2. the safety outcomes of bivalirudin and ticagrelor or bivalirudin and prasugrel combination at 2 and 30 days (Bivalirudin Registry).

Study population, randomization, and follow-up

The trial population will consist of patients who received a second-generation DES during primary PCI. The study flowchart is shown in Figure 1. The inclusion and exclusion criteria are shown in Table I. Patients that fulfill the inclusion and exclusion criteria will be enrolled after the primary PCI procedure. All patients will be followed during 6 months. At 6 months, patients that fulfill the randomization criteria (Table I) will be randomized in a 1:1 fashion to either stop or continue DAPT for an additional 6 months (to a total of 12 months after primary PCI). All randomized patients will be followed for 18 months (or 2 years after primary PCI), whereas patients that do not fulfill the randomization criteria will be excluded from the trial. The randomization will be delivered via sealed envelopes containing a computer-generated sequence produced by the coordinating Contract Research Organization (CRO).

Primary endpoints

DAPT-STEMI primary endpoint. The primary endpoint is a composite of all-cause mortality, any myocardial infarction (MI), any revascularization, stroke, and Thrombolysis in Myocardial Infarction (TIMI) major bleeding[5] (net adverse clinical events [NACE]) at 18 months after randomization. Definitions of the individual endpoint components are provided in Appendix A.

Resolute Integrity Registry primary endpoint. The primary end point will be the same as the primary end point of DAPT-STEMI at 30 days and 6 months.

Bivalirudin Registry primary end point. The primary end point will be a composite end point of all-cause mortality, MI, stroke, stent thrombosis (ST), and bleeding (following Bleeding Academic Research Consortium [BARC] definition[6]) at 2 and 30 days (see appendix A for definitions).

Secondary end points

DAPT-STEMI secondary end points. The major secondary end point will be a composite of all-cause mortality, any MI, stroke, ST, and TIMI major bleeding[5] at 9 and 18 months after randomization.

Other secondary end points are ST definite/probable (following ARC definition[7]), all-cause mortality, cardiac mortality, any MI, bleeding, and stroke, as well as target vessel MI, target vessel revascularization (TVR), target lesion revascularization (TLR), target vessel failure (TVF),

Table I. Inclusion and exclusion criteria

Inclusion criteria enrolment
STEMI patients between 18 and 85 years who underwent primary PCI with a second-generation DES implantation
Exclusion criteria enrolment
Intolerance to aspirin, prasugrel, ticagrelor, clopidogrel, heparin, bivalirudin, zotarolimus or everolimus
Known bleeding diathesis or known coagulopathy
Planned elective surgical procedure necessitating interruption of dual antiplatelet therapy during the first 6 months after randomization.
History of stent thrombosis
DES in main left coronary artery
Active bleeding, known bleeding diathesis, or known coagulopathy
Oral anticoagulant therapy with coumadin derivates
Malignancies or other comorbidity with a life expectancy of <1 year or that may result in protocol noncompliance
Pregnancy (present, suspected, or planned) or positive pregnancy test result (in women with childbearing potential, a negative pregnancy test results is mandatory)
Inclusion criteria randomization
Patients that are event-free and on DAPT at 6 months
Exclusion criteria randomization
Occurrence of death, MI, ST, and target vessel or any unscheduled revascularization during the first 6 months after inclusion, with the exception of (scheduled) revascularizations in nonculprit lesions performed within 45 days from the primary PCI
Stroke or bleeding or surgical procedure requiring discontinuation of DAPT during the first 6 months after inclusion
Oral anticoagulant therapy

and target lesion failure (TLF), evaluated at 9 and 18 months after randomization.

Resolute Integrity Registry secondary end points. The secondary end points will be identical to those of the secondary end points of DAPT-STEMI trial but measured at 30 days and 6 months.

Bivalirudin Registry secondary end points. The secondary end points will be ST (following ARC definition[7]), all-cause mortality, cardiac mortality, all MI and target vessel MI evaluated at 2 and 30 days, bleeding (following BARC definitions[6]) at 2 days, and stroke at 2 days.

Procedures and investigational treatment. At inclusion, all STEMI patients will be treated according to standard clinical practice. Artery puncture site is left to the discretion of the operator, although radial approach is strongly recommended to avoid bleeding complications at the puncture site. Thrombosuction and predilation of the lesion are left to the discretion of the operator. If clinically indicated and feasible, a PCI with stent implantation will be performed. The recommended stent device will be the Resolute Integrity (Medtronic, Santa Rosa, CA). Use of bivalirudin during primary PCI is strongly recommended. In accordance with revascularization guidelines,[8] DAPT, consisting of aspirin (ASA) 150-300 mg per os or 250-500 mg bolus intravenously followed by 75-100 mg daily, and prasugrel 60-mg loading dose followed by 10 mg daily or ticagrelor 180-mg loading dose followed by 90 mg twice daily will be initiated and continued for 6 months. Patients >75 years old and with a body weight of <60 kg will be treated with prasugrel 60-mg loading dose but followed by 5 mg prasugrel daily. Patient treated with clopidogrel will receive a 600-mg loading dose followed by 75 mg daily for 6 months.

At 6 months, patients will be randomized to either discontinue DAPT or continue DAPT for a further 6 months after randomization (12 months post–primary PCI) (Figure 1). Aspirin 80-100 mg daily will be continued indefinitely in all patients. DAPT compliance, medication use, and adverse events will be registered at 6 months (randomization) and at 24 months after primary PCI. Any interruption or termination, as well as the reason for this, will be documented. Noncompliance will be considered whether the patients voluntarily or involuntarily stopped the medication without any medical reason. Additional (scheduled) revascularizations in nonculprit lesions, when needed, should be performed within 45 days from the primary PCI; however, even in this case, the 6-month follow-up time point is based on the date of the primary PCI.

Ethics and informed consent. This study will be conducted according to the principles of the Declaration of Helsinki and in accordance with the Medical Research Involving Human Subjects Act. The patient will be informed of the possible participation in this trial before or during the PCI procedure, but enrollment will only take place after the PCI procedure is completed. Informed consent will be obtained after the PCI procedure in accordance with the Good Clinical Practice guidelines.

Statistical analysis

The trial is powered only for the primary end point. Analyses will be performed for both the intention-to-treat population and per-protocol. The primary end point will be based on intention-to-treat analysis.

The main analysis in this study will be Cox proportional hazards model. The hazards ratio (HR) and the upper limit of the 2-sided 95% CI for the HR for the period 0-18 months will be calculated by the Cox model. The HR over the follow-up period will be closely analyzed. If the proportional hazards assumption is violated, a Poisson model will be used in a secondary analysis.

The upper limit of the 2-sided 95% CI for the HR of 6-months DAPT after STEMI versus the standard of 12-months DAPT will be compared with the noninferiority limit. If the upper limit of the 95% CI for the HR is less than 1.66, "noninferiority" is declared.

Sample size calculation

The sample size was calculated under the assumption that the α value was .05 for a 2-sided test (.025 for a 1-sided test) with a power of 85% and a noninferiority limit of 1.66. The noninferiority limit is chosen to be 1.66 in this study; this limit is similar to or slightly larger than what was chosen in other recent trials comparing drugs or devices.[9-16] However, we have on purpose chosen a noninferiority margin based on HR plus the upper 95% CI and not a noninferiority margin based on an absolute percentage of a prespecified expected event rate because this implies that this prespecified event rate should be first reached before noninferiority can be claimed. Using a noninferiority margin based on HR of the observed events avoids this bias. Although 1.66 noninferiority margin might look large, it should be noted that this is only the upper limit of the 95%CI of the HR, and if the proportions in both arms were hypothetically exactly equal, the upper 95% CI of the relative risk (or HR) would be 1.33 and the upper 95% CI for risk difference would be close to 4%. This illustrates the impact of random fluctuation in a study like DAPT-STEMI.

The end point rate at 18 months postrandomization was assumed to be 15%. This assumption was based on 2-year result of the Resolute All-Comers trial[17] and Resolute All-Comers STEMI subgroup results[18] after excluding the event rates of the first 6 months. The sample size needed for these assumptions is 1,000. To compensate for the mortality and noncompliance to dual therapy in the first 6 months (before randomization), 1,100 patients should be enrolled after the PCI procedure.

Data analysis and reporting

Categorical variables will be assessed with the use of χ^2 or Fisher exact tests, whereas continuous variables will be expressed as mean ± standard deviation or median with range, and differences in outcome data will be statistically analyzed using parametric (Student *t*test) or nonparametric (Wilcoxon ranksum) tests as appropriate. For the DAPT-STEMI, occurrence of the primary end point at 18 months after randomization will be used for the main statistical analysis. The results in both groups for the primary end point as well as for the secondary end points will be presented as time to event curves (Kaplan-Meier).

We have not prespecified an economic analysis as part of the trial, mainly because this is an international trial and healtheconomics as well as reimbursement strategies are different in different countries. However, on the basis of the trial result, a post hoc analysis of the potential estimation of the cost-benefit of a shorter DAPT duration will be considered.

Discussion

Rationale for shorter DAPT duration after DES

Following concerns of a greater risk of stent thrombosis attributed to delayed stent endothelialization encountered with first-generation DES, DAPT was extended to 12 months after DES implantation on the basis of broad expert consensus,[19,20] irrespective of DES type and despite the absence of evidence-based randomized control trial (RCT) results. However, in the light of significant reduction in thrombotic events achieved from the novel second-generation DESs as compared with the first-generation DESs,[21] a shorter duration of DAPT can be contemplated.

Recent RCTs testing short DAPT duration (≤6 months) after implantation of first- and second-generation DESs showed that a short-DAPT strategy versus long-DAPT strategy (≥12 months) was noninferior in terms of composite primary clinical end point.[9-11,22-24] Interestingly, in the short-DAPT arms of these trials, the ischemic and/or thrombotic events were similar to the longer-DAPT regiment arms, therefore challenging the notion that 1-year of DAPT is necessary after DES implantation. Finally, recently, several RCTs failed to show survival advantage of prolonging (≥12 months) DAPT.[25-27] When considering these trials together, long-term DAPT showed a reduction of stent- and non–stent-related thrombotic events but an increase of major bleeding and a trend toward higher risk of all-cause mortality compared with standard regimen.[1]

DAPT duration after acute coronary syndrome

The recommendation of 12-month DAPT in patients with acute coronary syndrome (ACS) is based on the CURE[28,29] and CREDO[30] studies; however, the value of long-term treatment with clopidogrel post-PCI isolated from pretreatment was impossible to determine, and there was no significant advantage of clopidogrel over placebo after the first weeks following PCI in terms of death or MI.[31] Moreover, short-term (<12 months) DAPT compared with longer DAPT regimen reduced bleeding without increasing ischemic complications in studies

including patients with high-risk ACS,[32] or non-STEMI and STEMI.[33] However, the actual clinical evidence is limited and confounded mainly because those RCTs that enrolled a larger number of ACS patients (range 40%-75%) did not systematically use a second-generation DES,[10,23,24,34] whereas those that used exclusively second-generation DES enrolled only a small proportion of patients with ACS (range 24%-38%).[9,11,22] Furthermore, the percentage of the STEMI patients enrolled was very low. As STEMI was often an exclusion criterion.[9,10] Finally, none of these trials used the latest-generation P2Y12 inhibitors prasugrel (Effient) or ticagrelor (Brilinta).

Therefore the DAPT-STEMI trial results will provide important new information.

DAPT regimen

As already mentioned, the recommended DAPT in the study consists of ASA plus prasugrel or ticagrelor as suggested by the guidelines. However, the choice of the P2Y12 inhibitor is left to the physicians to reflect the current real-world practice in which still a portion of patients receive clopidogrel for economic and clinical (age, bleeding risk, etc) reasons. Considering the above-mentioned protocol's strong recommendation as well as the current guidelines for STEMI treatment, we expect that only a small proportion of patients will be treated with clopidogrel compared with the new P2Y12 inhibitors. Moreover, considering the large size of this trial, we expect that the percentage of patients receiving different P2Y12 inhibitors in the 2 arms of the study (short vs 12months of DAPT) would be well balanced. The potential different outcomes between the newer antiplatelet agents are not within the scope of this trial, and the trial is not powered for it; however, we would correct for differences between subgroups, might these be observed, in a multivariate analysis.

Finally, as DAPT will be stopped at 12 months even in the longer arm as per current guidelines, this study should not be considered as a long-term DAPT study.

Anticoagulation

As previously reported, the use of bivalirudin during primary PCI is strongly recommended as suggested by the guidelines.[35] Bivalirudin has proven safer in reducing bleeding and mortality in STEMI treatment when compared with heparin and GP IIb/IIIa inhibitors[36,37]; however, studies testing combination treatment of bivalirudin (Angiomax) with prasugrel or ticagrelor showed nonuniform results,[38-40] and therefore, additional data from the 2 prospective registers encompassed within the DAPT-STEMI trial will enrich the actual knowledge in this setting.

DAPT-STEMI primary end point

We chose to followup the patients for at least 1 year (18 months in the shorter DAPT arm) after the discontinuation of the DAPT taking into consideration not only stent-related thrombotic events due to the rebound phenomenon after P2Y12 discontinuation but also those events originating from non–infarct-related arteries which might also benefit from a longer DAPT. We opted to have a patient-oriented primary end point, and therefore, we chose to incorporate also any revascularization as one of the composites of the primary end point. Indeed, progression of coronary disease has been shown to progress by a repetitive process of atherosclerotic plaque rupture and healing[41] which may manifest as ACS or simply as progression of angina requiring revascularization, a process that is influenced by multiple factors, including DAPT.

In this sense, we could evaluate whether a longer DAPT compared with a short regimen may be able to influence the occurrence of events post–DAPT therapy having influenced a possible plaque progression during a prolonged DAPT regimen. On the contrary, if this is not true, a similar event rate during the follow-up period without DAPT regimen in both arms should be expected.

Resolute Integrity stent

We chose as the recommended stent the Resolute Integrity stent (Medtronic Vascular, Santa Rosa, CA), a second-generation thin strut cobalt-chromium stent that elutes zotarolimus from a 3-blend composed biocompatible permanent polymer coating with an improved stent frame design. Two large randomized studies have shown noninferiority for this stent against the criterion standard second-generation DES, the everolimus-eluting cobalt-chromium stent (EES).[42,43] Recent data from RCTs and RCT subanalyses have shown that the EES has an excellent safety profile, including in patients with STEMI, and shows improved outcomes as compared with bare metal stents as well as first-generation DESs.[44,45] Importantly, these studies have shown that STEMI patients treated with EES do not have a higher incidence of ST as compared with the rest of all-comer patients as previously believed. Only few data regarding clinical outcomes of STEMI patients treated with this second-generation stent are available; however, data from the Resolute All-Comers STEMI population show that this stent is at least as good as EES.[18] In this perspective, the prospective register of Resolute Integrity stent for use in STEMI would bring new insights on the outcomes of this new-generation DES in STEMI patient population.

Funding and trial registration

The DAPT-STEMI trial is registered on ClinicalTrials.gov (NCT01459627) and is approved by the local ethics committee. The trial is ongoing at investigative sites in the

Netherlands, Norway, Poland, and Switzerland. The trial has completed enrollment. August 2017 is the estimated data for final data collection and for primary outcome measure. The trial is funded by Maasstad Cardiovascular Research, Maasstad Hospital, Rotterdam, the Netherlands. The primary investigators and steering committee are solely responsible for the conduct of this study, all study analyses, the drafting and editing of the manuscript, and its final contents. More details on study organization are shown in appendix B.

Summary

The DAPT-STEMI trial is a prospective, randomized, multicenter, international-open label trial which aims to enroll 1,100 patients to assess whether restriction of DAPT therapy to 6 months post–primary PCI with second-generation DES is noninferior to the routine prolongation of such therapy to 12 months after intervention.

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