Impact of dual antiplatelet therapy after coronary artery bypass surgery on 1 year outcomes in the Arterial Revascularization Trial (ART).

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Abstract

Objectives: There is still little evidence to support routine dual antiplatelet therapy (DAPT) with P_2Y_{12} antagonists following coronary artery bypass grafting (CABG). The Arterial Revascularization Trial (ART) was designed to compare 10-year survival after bilateral versus single internal thoracic artery grafting. We aimed to get insights into the effect of DAPT (with clopidogrel) following CABG on 1 year outcomes by performing a post-hoc ART analysis.

Methods: Among patients enrolled in the ART (n=3102), 609 (21%) and 2308 (79%) were discharged on DAPT or aspirin alone respectively. The primary endpoint was the incidence of major adverse cerebrovascular and cardiac events (MACCE) at 1 year including cardiac death, myocardial infarction, cerebrovascular accident and reintervention; safety endpoint was bleeding requiring hospitalization. Propensity score (PS) matching was used to create comparable groups.

Results: Among 609-PS matched pairs, MACCE occurred in 34 (5.6%) and 34 (5.6%) in the DAPT and aspirin alone groups respectively with no significant difference between the two groups (HR 0.97; 95%CI 0.59-1.59; P=0.90). Only 188 (31%) subjects completed 1 year of DAPT and in this subgroup, MACCE rate was 5.8% (HR 1.11; 95%CI 0.53-2.30; P=0.78). In the overall sample, bleeding rate was higher in DAPT group (2.3% versus 1.1%; P=0.02) although this difference was no longer significant after matching (2.3% vs 1.8%; P=0.54).

Conclusions: Based on these findings, when compared to aspirin alone, DAPT with clopidogrel prescribed at discharge was not associated with a significant reduction of adverse cardiac and cerebrovascular events at 1 year following CABG.

Keywords: dual antiplatelet therapy; coronary artery bypass grafting; bleeding

Introduction

Coronary artery bypass grafting (CABG) is widely regarded as the revascularisation strategy of choice, particularly in patients with multivessel coronary artery disease [1]. However, CABG patients still have a significant risk of subsequent major adverse cardiovascular events (MACCE, including mortality, myocardial infarction (MI) stroke and repeat revacularization) secondary to graft failure and atherosclerosis progression, particularly during the first 12 months. In fact, MACCE rates in the first year after CABG still exceed 12% [2]

The appropriate antiplatelet regimen after CABG remains an area of controversy [3]. Dual antiplatelet therapy (DAPT) with the addition of an oral P_2Y_{12} antagonist such as Clopidogrel to aspirin for 1 year after surgery has been proposed to improve outcomes. Plaque stability, prevention of graft closure, and secondary thrombosis form the basis for using a second antiplatelet drug, whereas the increased risk of bleeding and lack of conclusive evidence should also be considered.

Evidence for use of DAPT following CABG [4] is based mainly on a small proportion of patients undergoing surgical revascularization in landmark trials enrolling acute coronary syndrome (ACS) patients [5-7]. Whereas cardiac surgeons are very familiar with the guidelines regarding discontinuation of DAPT prior to CABG to minimize bleeding risks [8,9], there is considerable variability in DAPT resumption in post CABG [10,11].

The Arterial Revascularization Trial (ART) was designed to investigate whether bilateral internal thoracic artery (BITA) grafting is associated with improved 10-year survival when compared to single internal thoracic artery (SITA) grafting in patients with multivessel disease undergoing CABG [12] and final results will be available in 2018. We aimed to get insights into the efficacy and safety of DAPT following CABG on 1 year outcomes by performing a retrospective analysis of the ART trial.

Materials and Methods

This research adheres to the principles set forth in the Declaration of Helsinki (http://www.wma.net/en/30publications/10policies/b3/index.html). For the purpose of the present analysis, patients enrolled in the ART (n=3102) were classified according to whether they were discharge on DAPT (with clopidogrel) or aspirin alone following surgery. In the ART, antiplatelet therapy prescribed at discharge was at discretion of responsible physicians. We excluded those who met the following criteria: 1) Hospital death; 2) Withdrawn; 3) No information on antiplatelet therapy at discharge; 4) Clopidogrel alone at discharge.

Trial design

The protocol for the ART has been published [13]. Briefly, the ART is a 2-arm, randomized multicenter trial conducted in 28 hospitals in 7 countries, with patients being randomized equally to SITA or BITA grafts. Eligible patients were those with multivessel coronary artery disease undergoing CABG including urgent patients. Emergency patients (on-going myocardial ischemia/cardiogenic shock) and those requiring single grafts or redo CABG were excluded.

Follow-up and Study Endpoints

Questionnaires were sent to study participants by post at 1 year after surgery. No clinic visits were planned apart from the routine clinical 6-week post-operative visit. Participants were sent stamped addressed envelopes to improve the return rates of postal questionnaires. Study coordinators contacted participants by telephone to alert them to the questionnaire's arrival and to ask them about medications, adverse events and health services resource use.

The primary endpoint was the incidence of major adverse cerebrovascular and cardiac events (MACCE) at 1 year defined as the occurrence of cardiovascular death (CV-death), myocardial infection (MI), either ST elevation or non ST elevation MI, cerebrovascular accident (CVA) or

repeat revascularization. We also investigated the composite endpoint of cardiac death, MI and CVA and all-cause mortality. Safety endpoint was bleeding requiring re-hospitalization. Adverse events were adjudicated blind to surgical procedure by a member of the Clinical Event Review Committee. Follow-up at 1 year was available for all patients included in the analysis (100%).

Statistical analysis

Multiple imputation was used to address missing data (http://www.jstatsoft.org/v45/i07/). Expectation-maximization with bootstrapping algorithm was used to generate 3 imputed datasets. No prior information was used. Sets of estimates from different datasets were combined using the Rubin rule: the central estimate corresponds to the mean of individual imputation estimates and the variance is the weighted sum of two variances: the within imputation variance and the between imputation variance [14]. Due to lack of randomization with regards to DAPT administration following surgery, a propensity score (PS) was generated for each patient from a multivariable logistic regression model based on pre-treatment covariates as independent variables with DAPT versus aspirin alone administration as a binary dependent variable [15]. Covariates included in the PS model were: age, female gender, body mass index (BMI), creatinine, diabetes mellitus (DM), smoking, chronic obstructive pulmonary disease (COPD), peripheral vascular disease (PVD), left ventricular ejection fraction (LVEF), left main disease (LMD), myocardial infarction (MI, including both ST elevation and non ST elevation MI), percutaneous coronary intervention (PCI), unstable angina (UA), off-pump CABG (OPCAB), use of saphenous vein graft (SVG), other medication prescribed at discharge: vitamin K antagonist (VKA), beta-blockers (BB), angiotensin converting enzyme inhibitor (ACEI) and angiotensin receptor blocker (ARB).

Pairs of patients were derived using greedy 1:1 matching with a calliper of width of 0.2 standard deviation of the logit of the PS (http://CRAN.Rproject.org/package=nonrandom). The quality of the match was assessed by comparing selected pre-treatment variables in propensity score–matched patients using the standardized mean difference (SMD), for which an absolute standardized difference of greater than 10% is suggested to represent meaningful covariate imbalance [16]. A Cox regression model, stratified on the matched pairs [14] and adjusted for other medications at discharge, was used to estimate the treatment effect (i.e. DAPT vs aspirin alone) on outcomes of interest (http://CRAN.R-project.org/package=survival). This approach accounts for the within-pair homogeneity by allowing the baseline hazard function to vary across matched sets. For competing risk adverse event (MI, CVA and repeat revascularization) a competing risk framework was used (https://CRAN.R-project.org/package=riskRegression). Potential effect modifiers (interaction terms) examined were: 1) unstable angina, 2) prior MI within 1 year; 3) prior percutaneous coronary intervention (PCI) within 1 year; 4) off-pump surgery; and 5) use of saphenous vein graft (SVG). Double robust method (multivariate adjustment in the PS matched sample) was used to compute treatment effect estimates within subgroups. The proportional hazard assumption was tested by graphical inspection using log(-log(S)) method with Kaplan Meier estimators from the PS matched sample. In this case, the space between the two curves should be constant over time (Supplementary Figure 1 for the primary endpoint). A goodness of fit test (Schoenfeld residuals) was used to confirm that residuals for the treatment variable were not related to time (P=0.49 for the primary endpoint). A generic binomial test was used for a post-hoc power calculation for the primary end-point. Time to event analysis were graphically presented as cumulative incidence curves which show the cumulative probabilities of experiencing the event of interest. Cumulative incidence was computed as $1\text{-}S_t$ where S_t corresponds to the proportion surviving past interval t) obtained from the life table using the Kaplan-Meier approach. All p-values <0.05 were considered to

indicate statistical significance. All statistical analysis were performed using R Statistical Software (version 3.2.3; R Foundation for Statistical Computing, Vienna, Austria).

Results

The final study population consisted of 2917 patients. Of them 609 (21%) and 2308 (79%) were discharged on DAPT or aspirin alone respectively. Baseline characteristics of the two groups are reported in Table 1. In particular, patients receiving DAPT were more likely to have unstable angina and to receive clopidogrel preoperatively. Patients discharged on DAPT were more likely to have off-pump surgery, to receive SVG and to be discharged on statins and ACEI/ARB. The use of vitamin K antagonists at discharge was higher in the aspirin group (Figure 1). After PS matching the two groups were comparable for all pre-treatment variables investigated (Figure 1).

Efficacy endpoints

Efficacy endpoints in the 609-PS matched pairs are reported in Table 2. The rate of MACCE was 34 (5.6%) and 34 (5.6%) in the DAPT and aspirin alone groups respectively with no significant difference between the two groups (HR 0.97; 95%CI 0.59-1.59; P=0.90; Figure 2 left). The rate of the composite of CV death, MI and stroke was 21 (3.5%) and 29 (4.8%) in the DAPT and aspirin alone groups (HR 0.71; 95%CI 0.40-1.27; P=0.20; Figure 2 right).

None of the possible effect modifiers showed a significant interaction with MACCE: unstable angina (β=-0.39±0.70; P=0.57); prior MI (β=0.1 ±0.87; P=0.98) or prior PCI within 1 year (β=-0.04±1.55; P=0.97), OPCAB (β=-0.82±0.69; P=0.23) and use of saphenous vein grafts (β=-0.35±0.97; P=0.71). However, unstable angina, OPCAB and the use of SVG showed larger coefficients in favor of a benefit from DAPT. In particular, in patients with unstable angina, DAPT did not significantly influence the risk of MACCE (HR_{DR} 0.90; 95%CI 0.40-2.06; P=0.81) but was associated with a lower risk for the composite of CV death, MI and CVA

(HR$_{DR}$ 0.42; 95%CI 0.15-1.21; P=0.1). In patients undergoing off-pump surgery, DAPT did not significantly influence the risk of MACCE (HR$_{DR}$ 0.90; 95%CI 0.50-1.63; P=0.73) but was associated with a lower risk for the composite of CV death, MI and CVA (HR$_{DR}$ 0.53; 95%CI 0.25-1.11; P=0.09).

Among 609 patients who received DAPT postoperatively, 188 (31%) completed 1 year of DAPT, 362 (59%) switched to aspirin alone and other 24 (4%) switched to Clopidogrel alone (unknown for the remaining 35 patients). The rate of MACCE and the composite of CV death, MI and CVA was 5.8% and 2.7% respectively for those who continued DAPT for 1 year, 3.9% and 1.7% respectively for those who switched to aspirin alone and 12.5% and 8.3% respectively for those who switched to clopidogrel alone. We the analysis was restricted to subjects who continued DAPT for 1 year (n=188), DAPT did not significantly influence MACCE (HR$_{DR}$ 1.11[0.53-2.30]; P=0.78) or the composite of death, MI and CVA (HR$_{DR}$ 0.62; 95%CI 0.22-1.69; P=0.34).

Post-hoc power calculation was based on a 2.0 percentage point reduction in MACCE (3.5% with DAPT vs 5.5% with Aspirin alone) accordingly to a pooled analysis recently published [3]. The power achieved was 90% (sample size 1218, 5% significance, 2 tails; Supplementary Figure 2).

Safety endpoint

The rate of major bleeding was significantly higher in patients discharged on DAPT (14/609, 2.3%) when compared to aspirin alone (25/2308, 1.1%) (HR 2.14[1.11-4.11]; P=0.02; Figure 3) although this difference was no longer significant after PS matching (14,2.3% vs 11,1.8%; HR 1.30; 95%CI 0.58-2.8; P=0.54).

Discussion

Based on the present post-hoc analysis there is no evidence that DAPT with Clopidogrel can significantly reduce the rate of MACCE following surgery. However, in subjects admitted with unstable angina and undergoing off-pump surgery, we found a non-significant trend towards a larger protective effect from DAPT. DAPT at discharge was associated with an increased risk of bleeding but bleeding rates were particularly low in both groups.

Definitive guideline recommendations regarding use of DAPT after CABG are currently lacking. Evidence for use of DAPT following CABG is based mainly on a small proportion of patients in three landmark trials enrolling ACS patients [17-19]. Those trials were not adequately powered to address the role of DAPT in the post-CABG cohort. Another limitation is that they studied three different oral P_2Y_{12} antagonists: Clopidogrel, Ticagrelor and Presugel. Moreover these results are based on post-randomization subsets from single RCTs in which DAPT was initiated prior to CABG. Therefore the decision to undergo CABG is a post randomization event occurring at variable times post randomization. This decision can thus be influenced by randomized group resulting in potential baseline imbalances between intervention and control groups. On the other hand, available trials on DAPT enrolling CABG patients only present limited design and are largely underpowered to detect significant differences [20-25].

Patients were enrolled into ART from 2004 to 2007 and Clopidogrel was the only P_2Y_{12} antagonist used in this trial. Prasugrel and Ticagrelor were approved for use in Europe 2009 and 2010 respectively and the question whether DAPT with newer P_2Y_{12} antagonists is more effective remains to be determined. Of note, a recent meta-analysis [3] including 4 CABG-subgroups ACS RCTs [17-20] (n=3901) and 5 post-elective CABG trials [21-25] (n=986) concluded that DAPT resumption with higher intensity P_2Y_{12} antagonists (Prasugrel or Ticagrelor), but not Clopidogrel, reduces all-cause mortality in ACS patients who have undergone

CABG. In the ART trial the vast majority of patients with prior MI within 1 year were discharged on aspirin alone in contrast with current recommendation to continue DAPT for one year following ACS regardless of the treatment adopted [4]. This might be partially explained by the fact that these recommendations have gained popularity after ART recruitment. We observed that subjects with unstable angina showed a larger benefit from DAPT although this result was not statistically significant. We also found that a non-significant trend toward better outcomes with DAPT in subjects undergoing off-pump surgery and those who received SVG but these subgroup analyses were largely underpowered to detect significant difference.

It has been demonstrated that off-pump CABG is associated with hypercoagulability postoperatively [26] which can affect graft patency rate in particular with saphenous vein graft. These patients may benefit more from DAPT than patients operated with conventional surgery although there is still paucity of evidence with conflicting results reported [24,27].

There are several limitations of the present study. Although a post-hoc power calculation suggested that the present analysis was sufficiently powered to detect a difference in the primary endpoint (MACCE at 1 year) between the two groups. Subgroup analyses including subjects presenting with unstable angina or receiving off-pump surgery or SVGs were largely underpowered. Despite PS matching, a residual imbalance cannot be excluded. In particular, we noticed that the rate of reintervention was higher in patients discharged on DAPT. This might partially due to higher prevalence of risk factors for further coronary interventions in this group. Finally only 31% of subjects initially prescribed on DAPT completed 1 year of treatment and this aspect might have underestimated the effect of DAPT. No data were available on DAPT duration in subjects who discontinued DAPT and therefore we were unable to discriminate the effect of short (3-6 months) versus long (1 year) DAPT. We performed a sensitivity analysis including only subjects who completed 1 year of DAPT and DAPT was con-

firmed to not be associated with better outcomes. We observed that the vast majority of bleeding occurred during the first two months from discharge thus supporting the hypothesis that also short term DAPT following CABG may increase the risk of bleeding.

In conclusion, based on these findings, there is no evidence of a significant benefit from DAPT with clopidogrel over aspirin alone following CABG. However, the present analysis was underpowered to investigate the effect of DAPT in high risk subgroups such as patients with ACS. Large prospective RCTs evaluating the use of DAPT post-CABG with higher intensity P_2Y_{12} antagonists are urgently needed to provide more definitive guidance for clinicians.

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Figures Legends

Figure 1. Standardized mean difference (SMD) for baseline variables before and after propensity score matching. (DAPT: dual antiplatelet therapy; SMD: standardized mean difference; PS: propensity score; BMI: body mass index; DM: diabetes mellitus; COPD: chronic obstructive pulmonary disease. PVD: peripheral vascular disease; MI: myocardial infarction; PCI: percutaneous coronary intervention; UA: unstable angina; LVEF: left ventricular ejection fraction; AF: atrial fibrillation; SVG: saphenous vein graft; OPCAB: off-pump coronary artery bypass; VKA: Vitamin K antagonist; BB: beta-blocker; ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker)

Figure 2. Cumulative incidence with relative 95% confidence bands of major cerebrovascular and cardiac events (MACCE, right) and of composite of cardiac death/myocardial infarction (MI) and cerebrovascular accident (left) in patients discharged on dual antiplatelet therapy (DAPT) or aspirin alone.

Figure 3. Cumulative incidence with relative 95% confidence bands of bleeding requiring hospitalization in patients discharged on dual antiplatelet therapy (DAPT) or aspirin alone.

Supplementary Figure 1. Proportional hazard assumption tested by graphical inspection using log(-log(S)) method with Kaplan Meier estimators from the matched sample.

Supplementary Figure 2. Graphical representation of post-hoc power calculation for the primary end-point.

Table 1. Baseline and operative characteristics of patients discharged on dual antiplatelet therapy (DAPT) or aspirin alone.

	DAPT	Aspirin (unmatched)	SMD	Aspirin (PS-matched)	SMD
n	609	2308		609	
Age (mean (sd))	62.9 (9.4)	62.9 (8.7)	0.006	63.3(8.4)	0.052
Female n(%)	73 (12.0)	331 (14.3)	0.070	78 (12.8)	0.025
BMI (mean (sd))	27.9(4.4)	28.3(3.9)	0.110	28.0 (4.0)	0.027
Creatinine (mean (sd))	101.2 (19.3)	95.1 (21.3)	0.301	101.2 (23.1)	0.001
DM n(%)	164 (26.9)	531 (23.0)	0.091	158 (25.9)	0.022
Smoking n(%)	86 (14.1)	334 (14.5)	0.010	75 (12.3)	0.053
COPD n(%)	47 (7.7)	131 (5.7)	0.082	42 (6.9)	0.032
PVD n(%)	49 (8.0)	152 (6.6)	0.056	50 (8.2)	0.006
Prior stroke n(%)	13 (2.1)	68 (2.9)	0.052	12 (2.0)	0.012
LVEF<.50 n(%)	136 (22.3)	582 (25.2)	0.068	141 (23.2)	0.020
LMD n(%)	112 (18.4)	498 (21.6)	0.080	134 (22.0)	0.090
MI within 1Y n(%)	149 (24.5)	541 (23.4)	0.024	156 (25.6)	0.027
PCI within 1Y n(%)	28 (4.6)	265 (11.5)	0.255	32 (5.3)	0.030
UA n(%)	252 (41.4)	726 (31.5)	0.207	236 (38.8)	0.054
Preop aspirin n(%)	534 (87.7)	1989 (86.2)	0.045	539 (88.5)	0.025
Preop clopidogrel n(%)	236 (38.8)	462 (20.0)	0.420	210 (34.5)	0.089
OPCAB n(%)	430 (70.6)	760 (32.9)	0.814	423 (69.5)	0.025
SVG n(%)	496 (81.4)	1751 (75.9)	0.136	491 (80.6)	0.021
N grafts (mean (sd))	3.3 (0.9)	3.1 (0.8)	0.224	3.3 (0.9)	0.038
Postop VKA n(%)	6 (1.0)	87 (3.8)	0.184	10 (1.6)	0.058
Postop BB n(%)	501 (82.3)	1949 (84.4)	0.059	501 (82.3)	<0.001
Postop Statins n(%)	581 (95.4)	2118 (91.8)	0.149	578 (94.9)	0.023
Postop ACEI/ARB n(%)	359 (58.9)	1130 (49.0)	0.201	348 (57.1)	0.037

DAPT: dual antiplatelet therapy; SMD: standardized mean difference; PS: propensity score; BMI: body mass index; DM: diabetes mellitus; COPD: chronic obstructive pulmonary disease. PVD: peripheral vascular disease; MI: myocardial infarction; PCI: percutaneous coronary intervention; UA: unstable angina; LVEF: left ventricular ejection fraction; AF: atrial fibrillation;

SVG: saphenous vein graft; OPCAB: off-pump coronary artery bypass; VKA: Vitamin K antagonist; BB: beta-blocker; ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker

Table 2. Outcomes in matched patients discharged on dual antiplatelet therapy (DAPT) or aspirin alone.

	DAPT	**Aspirin (matched)**	**DAPT effect***
N	609	609	
MACCE n(%)	34(5.6)	34(5.6)	0.97[0.59-1.59]
CV death/MI/CVA n(%)	21(3.5)	29(4.8)	0.71[0.40-1.27]
Mortality n(%)	7(1.2)	9(1.5)	0.78[0.29-2.1]
CV mortality n(%)	5(0.8)	8(1.3)	0.63[0.21-1.91]
MI n(%)	11(1.8)	13(2.1)	0.84[0.37-1.90]
CVA n(%)	9(1.5)	12(2.0)	0.75[0.31-1.78]
Repeat revascularization n(%)	17(2.7)	9(1.5)	1.91[0.85-4.33]

*Estimates obtained with Cox models stratified by PS-matched pairs and competing risk framework for MI, CVA and repeat revascularization.

DAPT: dual antiplatelet therapy; MACCE: major cardiac and cerebrovascular events; CV-death: cardiovascular death; MI: myocardial infarction; CVA: cerebrovascular accident

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